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The Cycloaddition of Allyl Cations to 1,3-Dienes: General Method for the Synthesis of Seven-Membered Carbocycles

New Synthetic Methods (40)

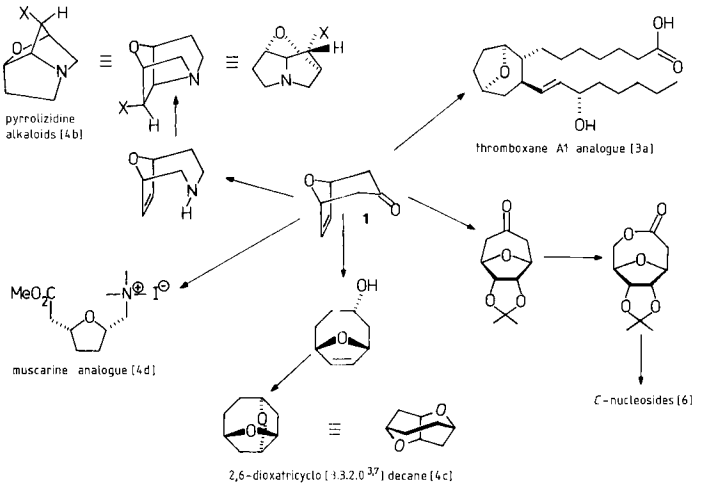
By H. M. R. Hoffmann*

The reaction of allyl cations and 1,3-dienes affords seven-, five-, and six-membered rings as well as products of electrophilic substitution and linear 1 : 1-adducts. In this review article, preparative and mechanistic advances are summarized with special emphasis on the synthesis of seven-membered carbocycles. For the first time, a comprehensive mechanistic description is presented: Three classes A, B, and C correlate product type and stereochemistry with the nucleophilicity of the diene, the electrophilicity of the allyl cation intermediate, and the donor capacity of the group Y attached to the central carbon of the allylic moiety. The problem "allylic resonance versus nucleophilic participation of Y" is discussed and experimental evidence is adduced for some participation of Y as a function of its nucleophilicity. For cyclopentenyl cations, enhanced charge separation and electrophilicity are postulated, even when Y is a good donor, due to the structurally enforced polarity of the π-allyl system.

1. Introduction

1.1. Preparative and Mechanistic Aspects

Common rings (ring size n = 5–7) with novel functionality and stereochemistry occur in many natural products and, for this reason alone, are of great interest. Because of ring strain and also for entropy reasons, seven-membered carbocycles are often more elusive and have been studied less actively than their lower homologues. They are also conformationally more flexible. Many of the compounds described here are bridged seven-membered cyclic compounds containing a five-membered ring or another bridge which more clearly defines overall shape and potentially mobile conformations. Some of the carbocyclic frameworks contain a plane of symmetry—which simplifies NMR spectra—and are aesthetically pleasing. Most importantly, the compounds have found wide application in synthesis. For example, 8-oxabicyclo[3.2.1]oct-6-en-3-one



Scheme 1. Selected transformations of 8-oxabicyclo[3.2.1]oct-6-en-3-one **1**.

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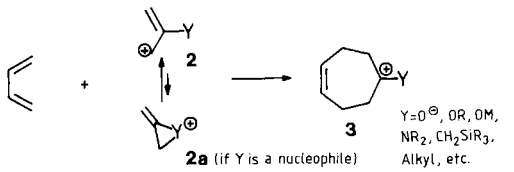
1, which is the prototype of the 2-oxopropano bridged 2,5-dihydrofurans and which we prepared for the first time in 1973[1], has served as starting material for the synthesis of a number of natural products and their analogues and also theoretically interesting molecules (Scheme 1). At least three, simple large-scale preparations of **1** have now been developed[2–4]. In this article I shall concentrate on progress made since the appearance of our first account[5]. The reaction of polybromoketones and carbonyliron compounds has been summarized by *Noyori*[6] and also by others[7].

Allyl cations such as **2** encompass many structural types and variations. Generally, Y is an atom or group which has the ability to stabilize positive charge in the product cation **3** or any other ring that may be formed. If Y is sufficiently nucleophilic, 1,3-interaction with the terminal carbon(s) may ensue with concomitant uncoupling of π-allyl overlap and formation of the cyclic valence tautomer **2a**. Reaction of π systems and **2a** — which is a perpendicular allyl cation if allyl resonance is lost completely—is a stepwise process.

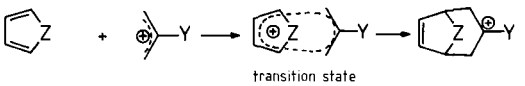


On the other hand, a planar delocalized allyl cation **2** is most likely when Y is less nucleophilic and also when planarity is structurally enforced, *e.g.* in cyclopentenyl-type cations. As we have shown, even the simple 2-methylallyl cation (Y = Me) reacts with cyclopentadiene and cyclohexadiene to give derivatives of **3**[8].

1.2. Classification of Allyl Cation Reactions with 1,3-Dienes

We have found it useful to divide reactions of allyl cations with 1,3-dienes into three categories, here exemplified for reactions of planar delocalized allyl cations and cyclic conjugated dienes.

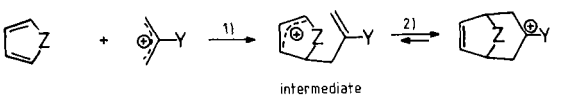
Class A. Concerted bond-formation



Predicted consequences:

1) Products: Bridged seven-membered rings.
2) Stereochemistry: Configuration of allylic cation remains intact. Transition state is "compact" or "extended" (see also Section 4.3.1).

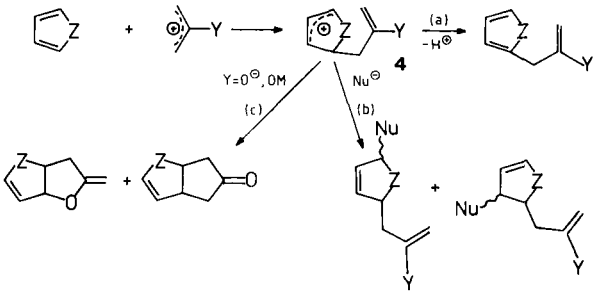
Class B. Stepwise bond-formation



Predicted consequences:

1) Products: Bridged seven-membered rings.
2) Stereochemistry: Configuration of allylic cation may be retained or lost, depending on the lifetime of carbocation **4** (see also Section 4.3.2).

Class C. Electrophilic addition followed by (a) loss of a proton with overall electrophilic substitution or (b) intermolecular- or (c) intramolecular-nucleophilic capture of 4



Predicted consequences:

Products: Five-membered carbocycles and heterocycles; acyclic 1:1-adducts via formation of one σ bond (see also Section 4.3.3).

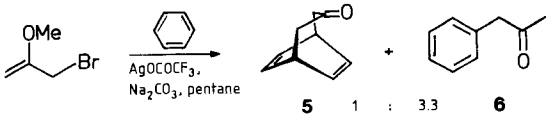
As far as a distinction between class A and class B is feasible, it must rely heavily on stereochemical and physical-organic arguments. From a kinetic viewpoint the class B/class C borderline depends on the rate constant for step 2) and its reverse, which in turn is determined by the lifetime and stability of carbocation **4**. However, the detection of short-lived intermediates such as **4** — let alone the determination of associated rate constants — is often cumbersome and ambiguous, even under favorable circumstances. Fortunately, the mechanistic background has clear phenomenological consequences in predicting a fairly wide range of products, which can generally be isolated and identified easily. Finally, each product type may be assigned to one or at most two of the three classes.

2. Methods for Generating and Capturing Allyl Cations; Survey and Applications in Synthesis

Experimental procedures for generating allyl cations are classified according to type of precursor and structure of electrophilic intermediate:

2.1. Allylic Halides and Lewis Acids

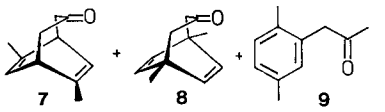
Heterolysis of allyl halides promoted by Lewis acids is the most direct route to allyl cations. The reaction is mechanistically simple, although the structure of electrophilic intermediate(s) may be in doubt when Y is nucleophilic and can interact with the allylic termini. Ambiguities due to ion-pairing may also encroach. The silver salt route remains perhaps the most useful and versatile procedure, especially when very reactive allyl cations are involved and all other methods and Lewis acids fail.



A key experiment which highlights the special driving force of 2-alkoxyallyl cation reactions[9], irrespective of mechanistic detail[10], is the addition of 2-methoxyallyl bromide to benzene to give bicyclo[3.2.2]nona-6,8-dien-3-one **5**. Because of the resonance energy of 36 kcal/mol, cycloadditions to benzene are rare. If the cycloaddition is to succeed, an allyl cation is apparently required which has the proper blend of electrophilicity at the terminal carbons and of nucleophilicity of Y (the simple 2-methylallyl cation **2**, Y = Me, reacts with benzene and furan to give products of electrophilic substitution, *i.e.* class C only). Toluene and *p*-xylene give lower yields of bicyclo[3.2.2]nona-6,8-dien-3-ones and more Friedel-Crafts type, *i.e.* class C, products.

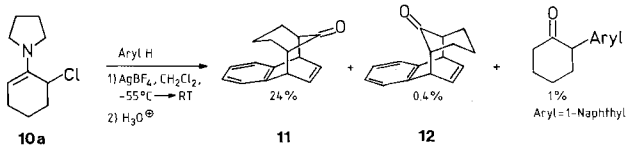
The resulting isomeric bicyclics form π-complexes of different strength with silver ions: For example, on non-aqueous work-up of the reaction mixture from *p*-xylene the remaining silver residues retain preferentially (71%) bicyclic diene **8**, which has two less hindered double bonds than its isomer **7** (Table 1). Parent dienone **5** has also been

Table 1. Product ratios for the silver trifluoroacetate-promoted cycloaddition of 2-methoxyallyl bromide to 1,4-dimethylbenzene [9].

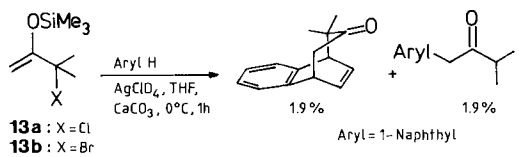


	[%]		
	7	8	9
Complete work-up	24	7	69
Work-up of Ag^+ residues only (anhydrous)	25	71	4

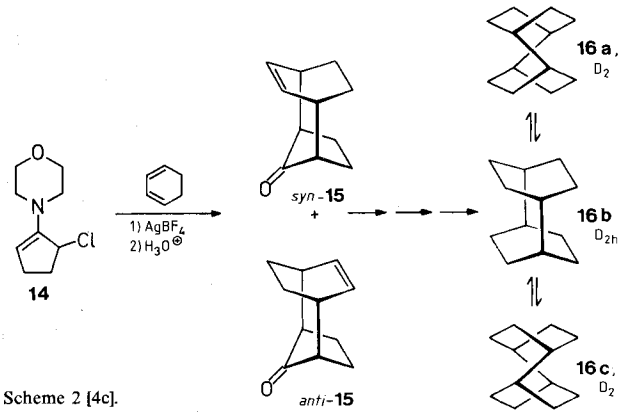
converted into the tricarbonyliron complex, albeit in low yield[5] (complexation of bicyclo[3.2.1]octa-2,6-dienes by silver ion is discussed in Section 2.2).



More recently, cycloadditions to naphthalene have been accomplished with varying success: The cyclic 6-chloroenamine **10a**[11a,b], in which electrophilic and donor strength are well balanced, is clearly superior to acyclic 2-siloxyallyl species **13a**[11c], because it gives not only more cycloadduct (**11** and **12**), but also less product of class C. However, attempts to trap benzene with **10a** and silver salts were not successful[11a,b].

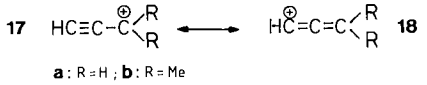


Cycloadditions with cyclopentenyl cations have remained difficult, one reason being the problem of obtaining suitable chloroenamines in reasonable yield. Using *Vilsmaier*'s 2-chloroenamine **14**[58a], *Ernst* and *Ganter* have

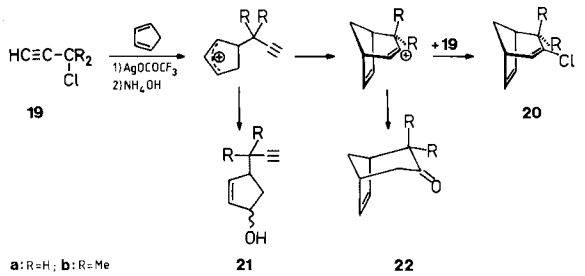


Scheme 2 [4c].

prepared **15** in 30% yield (*syn* : *anti* = 93 : 7)[12]. After hydrogenation and further steps, **15** was transformed into the novel hydrocarbon **16**, which may exist as the achiral D_{2h} conformer **16b** and also as the (presumably) more stable chiral twist conformer **16a** and enantiomer **16c**[12] (Scheme 2). Using the silver salt route *Mayr* et al.[13] have generated a variety of dehydroallyl cations (propargyl cations



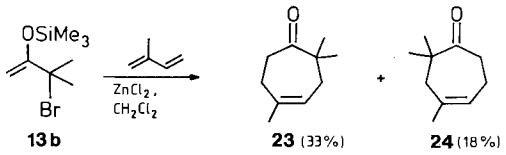
17 ↔ dehydroallyl cations **18**). Even **19a**, the educt from **17a** ↔ **18a**, reacted to give **22a** (7%). Because ions **17** ↔ **18** are likely to be linear, formation of the seven-membered



ring is a stepwise process (class B), which is also consistent with leakage into a product of class C, *i.e.* **21** (see Section 4.2). It should be noted that silver salts remove halide ions such as Br^- and I^- quickly and irreversibly by precipitating insoluble silver halides. Thus, there is no chance of an acid such as HHal being formed, which could destroy reactants and products alike. Furthermore, no free halide ion is generated which might intercept the allyl cation intermediate. Finally, at least for the generation of very reactive allyl cations such as 2-methylallyl, 2-methoxyallyl, and also **17a** ↔ **18a**, it is advisable to use $AgOCOCF_3$ instead of $AgBF_4$: Trifluoroacetate stabilizes the allyl cation, presumably via its weakly nucleophilic fluorine atoms, without significant collapse to covalent trifluoroacetic esters. Also if elimination occurs during the

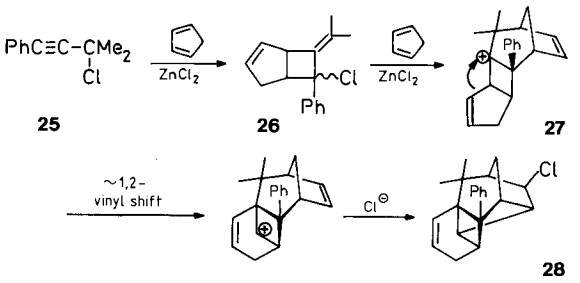
formation of cycloadduct, CF_3CO_2H is less harmful than the stronger acid HBF_4.

Mechanistically, the zinc halide induced heterolysis of allyl halides is related to silver ion induced heterolysis, although two terminal alkyl substituents—or one phenyl substituent—are generally required for ionization to occur. Since $ZnCl_2$ does not dissolve readily in CH_2Cl_2, it is helpful to prepare the ether adduct, which may be used at temperatures as low as -30 to $-50\,^{\circ}C$[14]. A simple example of the use of $ZnCl_2$ is the reaction of the isoprenoid building block **13b** with isoprene, which yields karahanaenone **23** and its isomer **24**[15]. These two monoterpenoids may also be obtained from the appropriate α,α'-dibromoketone with zinc/copper couple[16a] or triethyl borate/zinc dust[16b].



13b **23** (33%) **24** (18%)

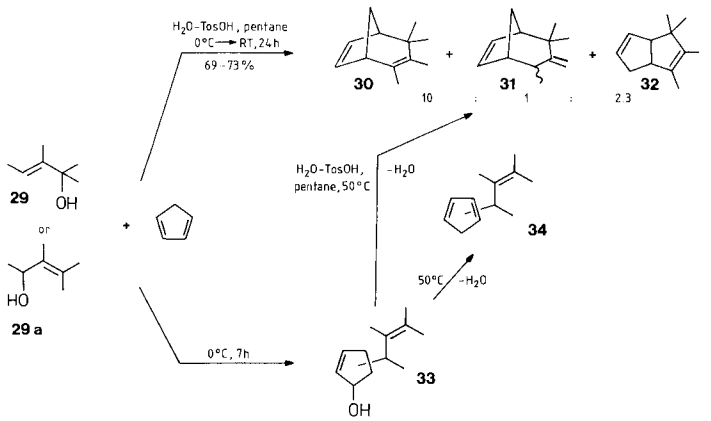
An unusual beginning and conclusion to an allyl cation reaction has been reported by *Mayr* et al.[17]: **26** is the 1:1-adduct of cyclopentadiene and propargyl chloride **25**; with excess cyclopentadiene adduct ion **27** is formed which, however, cannot easily lose a proton and instead rearranges to **28** (52% yield relative to **26**); the structure of **28** was secured by X-ray crystallography.



25 **26** **27** **28**

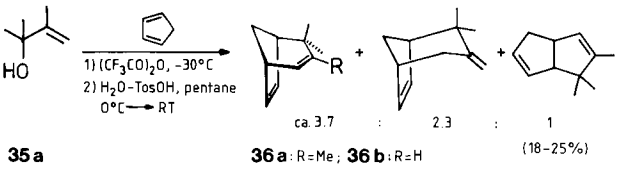
2.2. Activation of Allyl Alcohols and Related Compounds

Allyl alcohols with three terminal methyl groups, such as **29** and **29a**, react with cyclopentadiene under acidic two-phase conditions, *e.g.* in aqueous toluenesulfonic acid/pentane (Scheme 3). The reaction occurs, although cyclopentadiene is acid sensitive in homogeneous solution, to form



Scheme 3 [18].

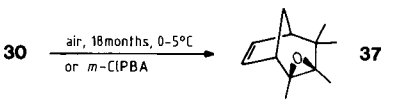
dicyclopentadiene and notorious blue-black polymers. The ratios and yields of adducts **30** and **32** are similar to those observed in the silver salt reaction of the corresponding allylic halide precursor. When the two-phase reaction is run at 0°C and interrupted, allyl-substituted cyclopentenols of type **33** can be isolated, *i.e.* products of class C. Interestingly, on being exposed to aqueous acid/pentane at 50°C, these isomeric cyclopentenols again give **30** and **31** (class B) and **32** (class C)[18].



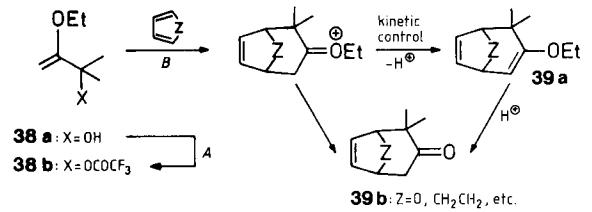
35a **36a**: R=Me; **36b**: R=H

2,3-Dimethyl-3-buten-2-ol **35a**, which clearly is more reluctant than **29** or **29a** to form an allyl cation under standard two-phase conditions, can nevertheless be used by means of a simple trick. On being shaken with trifluoroacetic anhydride at $-30\,^{\circ}C$, it forms the trifluoroacetic ester which on warming with cyclopentadiene under acidic two-phase conditions affords **36a** as the major product. Furthermore, the *exo*-methylene compound and [3.3.0]bicycle corresponding to **31** and **32**, respectively, are now relatively more important products[19].

2,3,4,4-Tetramethylbicyclo[3.2.1]octa-2,6-diene **30** is oily and sensitive to oxygen. On contact with air the crystalline *exo*-epoxide **37** is slowly formed, which can be obtained



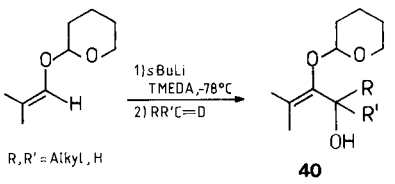
more quickly by epoxidation of **30** with *m*-chloroperbenzoic acid (*m*-ClPBA). A useful method for isolating, purifying and storing strained bicyclo[3.2.1]octa-2,6-dienes such as **30** and **36a,b** is complexation with silver ions. The silver nitrate complex of **30**, *i.e.* $(C_{12}H_{18})_2AgNO_3$ is crystalline (m.p. = 114—115 °C) and can be isolated directly from the mother liquor of the two-phase reaction (Scheme 3). The bicyclic diene **36b**, which has a much less hindered second double bond than **30**, forms a 1:1-complex with $AgNO_3$, *i.e.* $(C_{10}H_{14})AgNO_3$, m.p. = 153 °C. Other complexes, *e.g.* that of **36a** and $AgNO_3$, have a stoichiometry lying between 2:1 and 1:1, *ca.* 1.5:1[20]. Bicyclo[3.2.1]octa-2,6-dienes have served inter alia as model compounds for 9,10-dehydronorzizaenes **46**.



Scheme 4. *A*: $(CF_3CO)_2O$, $EtN(iPr)_2$; *B*: $ZnCl_2$, $EtN(iPr)_2$ (cf. [21]).

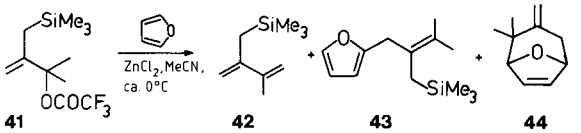
The tertiary allylic alcohol **38a** is readily accessible from pyruvic acid, but is slow to form an ester with common acylating agents, *e.g.* acetic anhydride/pyridine, or with tosylating agents (tosyl chloride/pyridine). Again, trifluoro-

acetic anhydride is a potent acylating agent which reacts with **38a** at −40 °C and below, even in the absence of catalytic 4-dimethylaminopyridine. The resulting trifluoroacetic ester **38b** has been ionized under a variety of conditions. With cyclic 1,3-dienes and in the presence of hindered amine, we have obtained novel bicyclic enol ethers **39a**, *i.e.* products of kinetic control, rather than the thermodynamically more stable bridged cycloheptenones **39b**. Because enol ethers such as **39a** are acid-sensitive, the reaction medium must at least be neutral or even weakly basic. 2-Ethoxyallylic alcohol **38a** is probably more advantageous than the corresponding 2-methoxyallylic species here, because dealkylation of intermediate oxonium ion appears to be less facile; and perhaps also because an ethyl enol ether is more nucleophilic than a methyl enol ether (Scheme 4)[21].



40

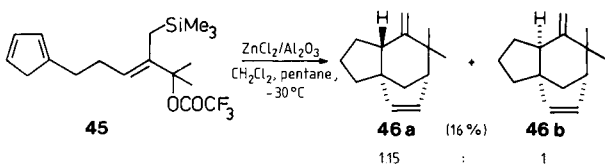
A variety of 2-alkoxyallyl alcohols, *e.g.* of type **40**[22], have also been prepared by oxygen-directed lithiation of enol ethers and subsequent trapping of the vinyllithium intermediate with aldehydes and ketones (TMEDA = tetramethylethylenediamine.)



41 **42** **43** **44**

1 : 6 : 3

The cation derived from educt **41** is much more sensitive toward deprotonation than 2-alkoxyallyl and metal oxyallyl cations (cf. also Section 4.1.1). Thus, in the presence of amine, diene **42** is formed easily from **41**. Nonetheless, in the absence of hindered amine at 0 °C and below, the reaction of **41** with furan has sufficient driving force for formation of bridged methylenetetrahydropyran **44** (class B), in addition to the more conventional products **43** (class C) and **42**[23]. Summing up, the trifluoroacetate method leaves us free to generate structurally complex allyl cations late in a synthesis and also in the presence of other sensitive functionalities. Perhaps the most demanding example described by us so far is the intramolecular "chromatographic cycloaddition" of **45** which was accomplished at

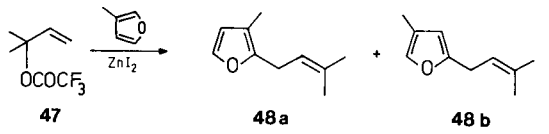


45 **46a** (16%) **46b**

1.15 : 1

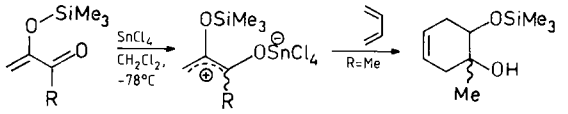
−30 °C and below on an alumina column coated with $ZnCl_2$. A short route to 9,10-dehydro-2-norzizaene **46** and related sesquiterpenes has therefore been opened up[24].

Class C reactions of furans, *e.g.* the formation of **43**, are not necessarily a nuisance, but may be preparatively useful. For example, the reaction of 3-methylfuran with **47** is a simple prenylation, yielding rosefuran **48a** and its hi-



47 **48a** **48b**

therto unknown isomer **48b**[25]. Generally, Friedel-Crafts type alkylations of furans are now feasible using the new methodology for generating sensitive carbocations. It has

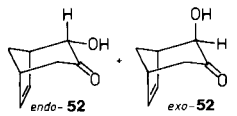
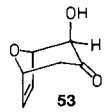


49a: R = H
49b: R = Me

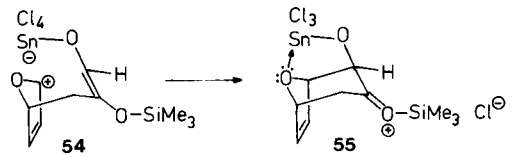
50

been reported recently that 2-siloxyacrolein **49a**, but not the less electrophilic **49b** (R = Me), serves as the 1-hydroxy-2-oxidoallyl synthon **50** in the presence of equimo-

Table 2. Reaction of dienes with 2-siloxyacrolein **49a**/$SnCl_4$ as allyl cation component in CH_2Cl_2 at −78 °C [26].

Diene	*t* [h]	Cycloadduct	Yield [%]
	2–3	**51**	32
	5	 *endo*-**52** *exo*-**52**	72
	1–6	 **53**	43

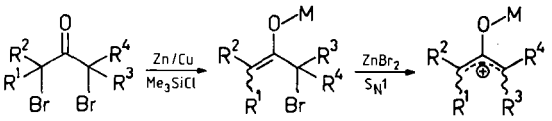
lar amounts of $SnCl_4$ (Table 2). Interestingly, furan affords only the *exo*-adduct[26]. The stereoselectivity can be explained by postulating that the cycloaddition belongs to class B, formation of the second σ bond being late or product-like and being aided by chelation of oxygen (**54** → **55**).



54 **55**

2.3. α,α′-Dihaloketones and Reducing Agents

α,α′-Dihaloketones **56** and reducing agents such as zinc/copper couple generate an α-halogenated zinc enolate of type **57** and subsequently the zinc oxyallyl cation of type **58**. Again, the S_N1-like ionization of **57** to **58** is promoted by $ZnBr_2$ formed in situ, and which may also be added at the outset. The reaction of **56** with zinc/copper couple has

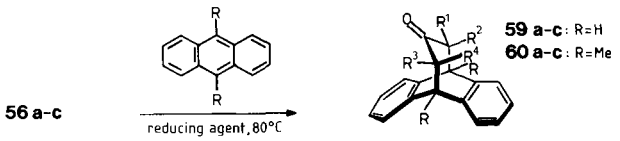


56 57 M = ZnBr, $SiMe_3$, Na 58

	R^1	R^2	R^3	R^4
a	H	Me	H	Me
b	H	Me	Me	H
c	Me	Me	Me	Me
d	H	Br	H	Br
e	H	Me	H	H
f	Me	Me	H	H
g	H	*i*Pr	H	*i*Pr

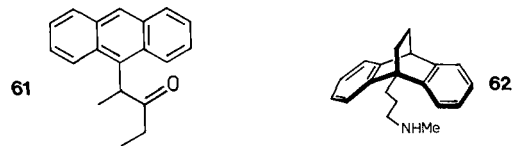
been accelerated and yields have been increased by addition of Me_3SiCl, which leads to formation of the α-halogenated trimethylsilyl enol ether of type **57** and thence to cation of type **58**, which is more electrophilic than **58**, M = ZnBr.

Even catalytic amounts of Me_3SiCl are sufficient, indicating that Me_3SiCl or Me_3SiBr are regenerated during the reaction cycle; in fact, with acid-sensitive dienes such as cyclopentadiene it is advisable to use a relatively small amount of Me_3SiCl[27].



56 a-c — reducing agent, 80°C → **59 a-c**: R = H; **60 a-c**: R = Me

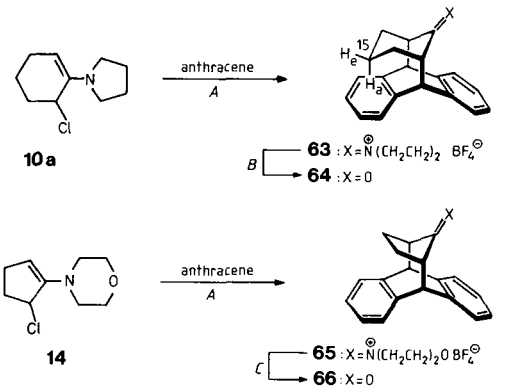
The reaction of α,α′-dibromoketones **56** and reducing agents with anthracene has been studied under three sets of conditions (Table 3)[27,28]. The most electrophilic oxidoallyl species (see Section 4.2), *i.e.* iron oxyallyl, gives somewhat higher yields than siloxyallyl, which in turn is much more effective than zinc oxyallyl. Since anthracene and 9,10-dimethylanthracene are not particularly nucleophilic, it is understandable that the high electrophilicity of the allyl cation is important here. The reaction of **56a,b** with zinc/copper couple and anthracene affords *ca.* 1% of **61** (class C). This fact and the formation of 10% of the *trans* isomer **59b** within the *cis-trans* mixture of isomers **59a** and **59b** suggests that the reaction is on the class B/class C borderline (cf. also Section 4.3.2).



9,10-Propanoanthracene derivatives such as **59** and **60** are structurally related to maprotiline® **62**, a clinically successful antidepressant developed by Ciba-Geigy[29]. Adduct **60c** is unusual in having two CC bonds between two quaternary carbon atoms. Its crystal structure has been determined and is discussed in Section 3.1 (Fig. 1).

Reactions of cyclic allyl cations are generally more demanding preparatively than those of acyclic allyl analogues. In fact, most of the work in this area has been carried out with furan, which also functions as the solvent.

α,α′-Dibromocycloalkanones—which are especially reactive when they are five- and six-membered derivatives—and anthracene react poorly with a variety of reducing agents, and it is advisable to return to preformed allylic species and silver salts (Section 2.1). In his dissertation, *R. Schmid*[11a] has shown that in the presence of $AgBF_4$ and anthracene, cyclic α-chloroenamines **10a** and **14** afford iminium salts **63** and **65**, respectively (Scheme 5). **14** is the only accessible chloroenamine of cyclopentanone at present; it is sensitive and must be used without distillation (*ca.* 60% purity by NMR). Remarkably, the sterically hindered iminium salt **65** is almost inert toward hydrolysis, formation of **66** requiring extreme conditions; on being refluxed



10a — anthracene, *A* → **63**: X = $\overset{\oplus}{N}(CH_2CH_2)_2$ $BF_4^{\ominus}$; *B* → **64**: X = O

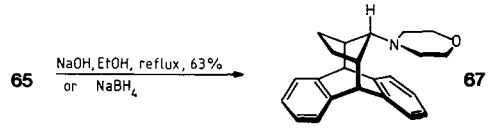
14 — anthracene, *A* → **65**: X = $\overset{\oplus}{N}(CH_2CH_2)_2O$ $BF_4^{\ominus}$; *C* → **66**: X = O

Scheme 5. *A*: $AgBF_4$, CH_2Cl_2; *B*: 1 N NaOH, MeOH (3:2), 24 h reflux (cf. [11a, b]); *C*: 1 N NaOH, DME, 6 h reflux (cf. [11a, b]). Yields: **63**: 77%; **64**: 76–87%; **65**: *ca.* 35%.

Table 3. Reductive dehalogenation of α,α′-dibromketones **56** and intermolecular cycloaddition to anthracene and 9,10-dimethylanthracene [27, 28]. (For structure of **60c** see also Fig. 1 in Section 3.1.)

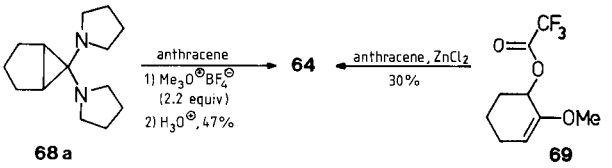
Educt	R^1	R^2	R^3	R^4	R	Product	Yield [%] in reduction with Zn/Cu	Zn/Cu/Me_3SiCl	$Fe_2(CO)_9$
56a,b [a]	H	Me	H	Me	H	**59a**	22 [b, c]	93 [d]	88 [b]
	H	Me	Me	H		**59b**			
56c	Me	Me	Me	Me	H	**59c**	3	71	90
56a,b [a]	H	Me	H	Me	Me	**60a**	8 [e]	—	86 [e]
	H	Me	Me	H		**60b**			
56c	Me	Me	Me	Me	Me	**60c**	<2	40	76

[a] **56a** and **56b** are diastereomers which cannot be distinguished in this reaction. [b] Ratio **59a** : **59b** = 90 : 10. [c] *Ca.* 1% of **61** was isolated after chromatography. [d] Ratio **59a** : **59b** = 1 : 1 (equilibrium ratio). [e] Ratio **60a** : **60b** = 95 : 5.



65 — NaOH, EtOH, reflux, 63% or $NaBH_4$ → **67**

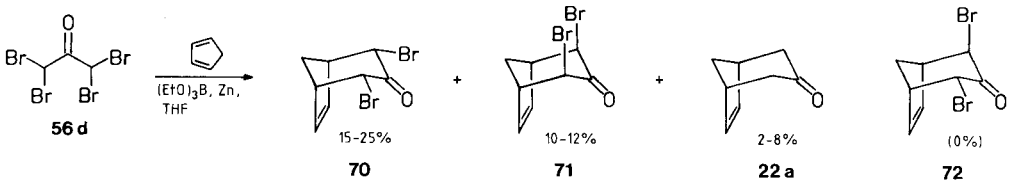
with ethanolic NaOH, **65** does not form **66**, but amine **67**, which can be prepared more readily by reduction of **65** with $NaBH_4$. The mechanism of the reaction of **65** with NaOH is not clear at present. Adduct **64** has also been

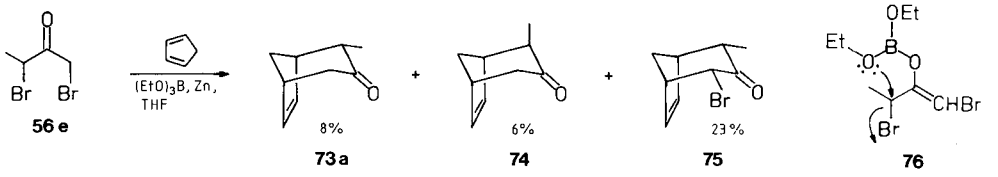


68a **69**

prepared in 46.5% yield using the less electrophilic bicyclic aminal **68a** and $Me_3O^+BF_4^-$[11a,b], and in *ca.* 30% yield from **69** and $ZnCl_2$[30]; in this case anthracene/$ZnCl_2$ and Hünig's base [$EtN(iPr)_2$] were refluxed in CH_2Cl_2 for 30 h, while **69** was slowly added dropwise. The chemistry of the novel double-decker compounds **63**—**67** has hardly been explored. **64** and the corresponding naphthalene adduct show interesting ^{1}H-NMR properties. In **64**, the signals of protons H_e—C(15) and H_a—C(15), which are situated immediately above the aromatic π system, are shifted to high field and appear as broad multiplets at $\delta = 0.8$ and -0.4, respectively (signal width 35—40 and 55—60 Hz, respectively)[11a,b].

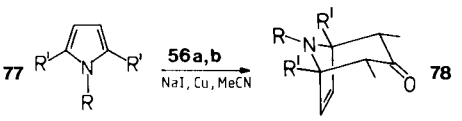
Since siloxyallyl cations, *e.g.* **58**, M = $SiMe_3$, can be generated from α,α′-dibromoketones it is not surprising that boron oxyallyl cations have also been used, even before the current activity on boron enolates in the aldol reaction began. Usually, at least two alkyl groups are required for the generation of metal oxyallyl cations **58** from α,α′-dibromoketones **56** (cf. also Table 3). Important exceptions





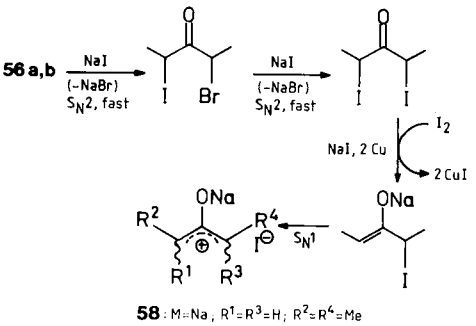
to this rule are reactions of polybromoketones, *e.g.* **56d**, which reacts with triethyl borate, unactivated zinc dust, and cyclopentadiene to give **70**, **71**, and **22a**; **72** is not formed. Brominated products **70** and **71** may be reduced to **22a**. The triethyl borate/zinc procedure is especially useful for structurally simple species including 1,3-dibromo-2-butanone **56e**. Because of the formation of *mono*-debrominated adducts, *e.g.* **75**, from dibromoketone **56e**, the reaction presumably involves initial proton loss from **56e** and formation of boron enolate **76**, which goes on to ionize with intramolecular assistance by oxygen. Consistently, attempts to use tetraalkylated α,α′-dibromoketones, *e.g.* **56c**, which cannot form a boron enolate by proton loss, were not successful[3b].

α,α′-Dibromoketones have also been reduced by iodide ions, especially from sodium iodide, in the presence of metallic copper as a scavenger for the molecular iodine formed. This procedure has been useful in mechanistic studies (Section 4.3) and also in reactions with electron-rich dienes, such as simple pyrroles (**77** → **78**)[31]. The pos-



a R=H, R′=Me;
b R=Me, R′=H

tulated reactive intermediate is sodium oxyallyl **58**, M = Na (Scheme 6)[32]. By comparison, the corresponding zinc oxyallyl species (from **56a,b** + Zn/Cu) and lithium

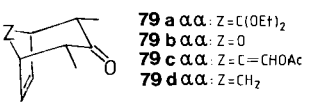


58: M=Na, $R^1=R^3=H$; $R^2=R^4=Me$

Scheme 6. Intermediates in the reaction of **56a,b** with NaI/Cu.

oxyallyl species (from **56a,b** + LiI/Cu) are more electrophilic than **58**, M = Na, and react with pyrroles **77** to give products of class C, *i.e.* electrophilic substitution. If zinc oxyallyl and iron oxyallyl are to react with pyrroles in a manner analogous to the formation of **78a,b**, the substituent R on nitrogen in **77** must be electron-attracting, *e.g.* R = CO_2Me, in order to slow down fragmentation [class B, reverse of step 2)].

The NaI/Cu procedure has also been carried out with the two-phase system acetonitrile/pentane for the capture of the reactive 5,5-diethoxycyclopentadiene (which is prone to dimerization via Diels-Alder reaction) to afford *cis*-diequatorial **79aαα**[32]. A detailed procedure for the

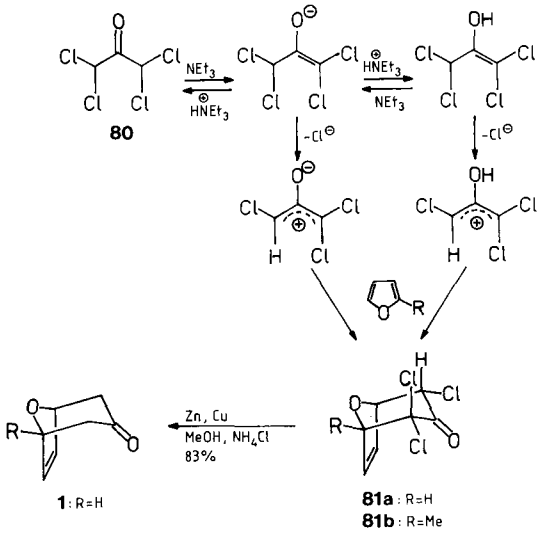


79a αα: Z = $C(OEt)_2$
79b αα: Z = O
79c αα: Z = C=CHOAc
79d αα: Z = CH_2

preparation of **79bαα** has been published in Organic Syntheses[33]. Finally, reaction of 6-acetoxyfulvene affords not only **79cαα**, but also some αβ-isomer (αα : αβ = 5.2 : 1; class B, Section 4.3.2)[32].

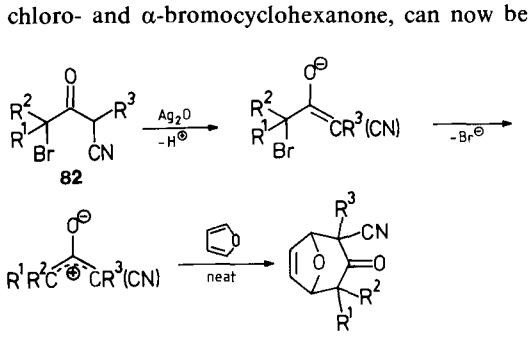
2.4. α-Haloketones and Bases

Although α-monohaloketones are less expensive and easier to handle and prepare than α,α'-dihaloketones, the doubly activated dibromoketones have until recently been much more important preparatively than their singly activated analogues. However, as shown by *Föhlisch,* in particular, α-monohaloketones do have a useful role to play, especially in reactions with electron-rich furans, which may be used in excess, *e.g.* as a co-solvent.



Commercially available 1,1,3,3-tetrachloro-2-propanone **80** or its tetrahydrate reacts with a methanolic solution of furan at room temperature in the presence of triethylamine to give **81a** in 54% yield, which in turn can be reduced to **1**. This sequence is probably the most economic route to **1** at present. With 2-methylfuran, **81b** is formed regioselectively[2], consistent with a class B process in which the less encumbered CC bond is formed in the first, intermolecular step to give the more stable intermediate.

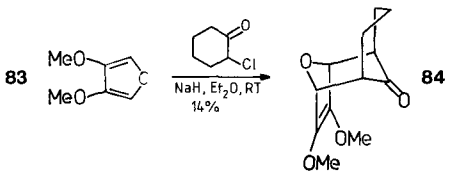
However, for a number of monohaloketones reactions in methanol are slow and hence the latter may compete with furan for electrophilic intermediates. By using 2,2,2-trifluoroethanol (TFE) as solvent—which is much less nucleophilic and has high ionizing power—and triethylamine or sodium 2,2,2-trifluoroethoxide as base, the yields of cycloadducts increase; cyclic α-haloketones, such as α-chloro- and α-bromocyclohexanone, can now be used[34].



Scheme 7.

α-Bromoketones also react with $AgBF_4/NEt_3$ in acetonitrile or neat furan[35], and the more acidic γ-bromo-β-oxonitriles **82** have been dehydrohalogenated with Ag_2O[36] (Scheme 7). A recent variant uses inexpensive $LiClO_4/NEt_3$ in diethyl ether. The progress of the reaction can be monitored by following the precipitation of $NEt_3H^+Cl^-$ or $NEt_3H^+Br^-$, which are insoluble in the reaction medium[37]. Presumably, relatively electrophilic lithium oxyallyl cations (**58**, M = Li) are intermediates in this reaction, because leakage into products of extended attack is quite noticeable (see also Section 4.3.1).

Perhaps the most nucleophilic diene investigated to date, which necessarily must be captured by a very weakly electrophilic allyl cation equivalent if a class C reaction is to be avoided, is the highly sensitive 3,4-dimethoxyfuran



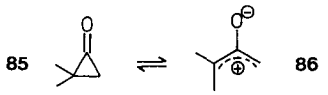
83. Using α-chlorocyclohexanone and the strong base NaH, *Eugster* et al.[38] have prepared **84** in 14% yield.

Summarizing, the base-induced reaction of α-haloketones tends to generate weakly electrophilic intermediates which react specifically with furan and other nucleophilic dienes (see Section 4.3.2 for the special case of **148**).

2.5. Cyclopropanones and Related Species

2.5.1. Cyclopropanones

Cyclopropanones and their cycloadditions are of theoretical interest, but for work on a preparative scale these small ring compounds are impractical, because they are not generally accessible and are too difficult to handle. 2,2-Dime-



thylcyclopropanone **85** is obtained readily from dimethylketene and diazomethane and has been studied most thoroughly: it adds to furan, cyclopentadiene, 6,6-dimethylfulvene, and the relatively nucleophilic *N*-methylpyrrole, but fails to react with anthracene and, of course, butadiene[39]. Parent cyclopropanone cannot be used; in this respect it is similar to the unsubstituted allene oxide (Section 2.5.2) and to 1,3-dibromopropanone/Zn[5] or $Fe_2(CO)_9$[6], but is *unlike* 2-alkoxyallyl bromide/$AgOCOCF_3$[1,9]. The reactive intermediate in cycloadditions involving cyclopropanones—if there is an intermediate—is unlikely to be a planar oxidoallyl cation such as **86**. One reason is that the separation of positive and negative charge in **86** would be energetically too costly (cf. also **148**). An 8-electron transition state with Möbius geometry[5] remains an attractive possibility for concerted cycloadditions of cyclopropanones to dienes. Such a transition state would also be consistent with the failure of cyclopropanones to react with less nucleophilic dienes such as anthracene and butadiene.

2.5.2. *Allene Oxides (Methyleneoxiranes)*

A variety of allene oxides (methyleneoxiranes) have been generated, studied, and characterized in recent years. These highly reactive heterocycles serve as a crude model for a completely bridged ion **2a** and, like the valence tautomeric cyclopropanones, may cycloadd to dienes provided that the developing positive charge can be sufficiently stabilized by substituents. For **87c**, seven-membered adducts have been prepared with cyclopentadiene (**87c** → **73c**), furan, and methyl-1-pyrrolecarboxylate (Table 4). **87a** and cyclopentadiene do not afford **73a**, but instead the product of electrophilic substitution **88a**[40]. This is in contrast to 2-methylcyclopropanone, which cycloadds to cyclopentadiene and furan, although probably in low yield[39]. The regioselectivity of the reaction of cyclopentadiene with **87a** and **87b** is not in accord with a planar oxidoallyl intermediate (cf. also **86**), which should be attacked at the *less* alkylated terminus in a late, product-like transition state. Rather, cyclopentadiene behaves as a nucleophile and attacks the quite electrophilic carbon of the highly strained allene oxide ring[40].

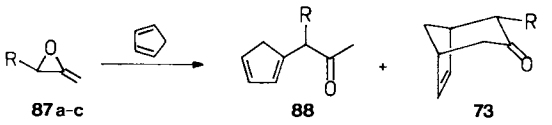
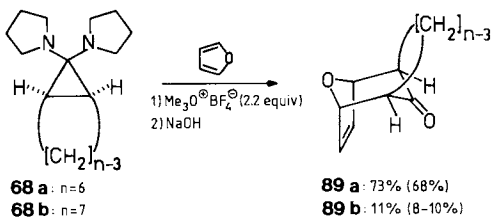


Table 4. Yields in the addition of methyleneoxiranes **87** to cyclopentadiene.

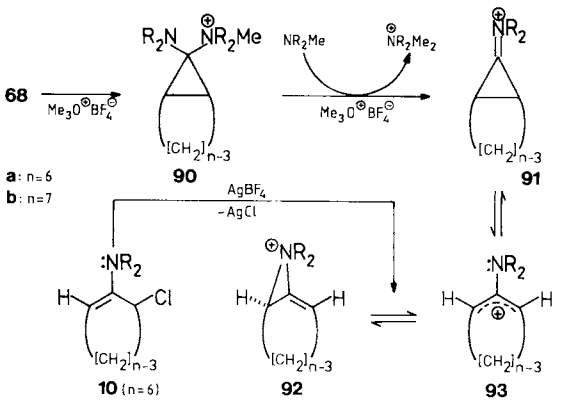
	R	Yield [%] 88	73
a	Me	30	—
b	*i*Pr	48	—
c	Ph	—	66

2.5.3. *Bicyclic Aminals*

The generation of cyclic 2-aminoallyl cations using silver salts has been described in Section 2.1. In his dissertation, *R. Schmid*[11a] has reported a second approach starting from closed, cyclopropyl cation type precursors, *i.e.* bicyclic aminals. Although both procedures may appear to be very similar mechanistically, the silver salt route affords a *higher* yield of cycloadduct **64** with anthracene (cf. **10a** in Scheme 5 as well as **68a**). With the more nucleophilic furan, yields are the same for both procedures (Scheme 8). At first sight, this difference may seem surprising. However, by starting from the monocyclic precursor **10a** and $AgBF_4$, the potentially more electrophilic valence tautomers **92** and **93** are reached earlier than by starting from the bicyclic precursor **68**. In other words, the electrophilicity of the allyl cation intermediate is again crucial for cycloadditions to anthracene—which does not add to less electrophilic cyclopropanones (Section 2.5.1)—but less so for reactions with furan.



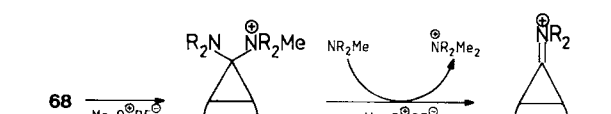
Scheme 8. Tricycles **89** from bicyclic aminals **68** and furan. (Yields in parenthesis refer to α-chloroenamine/$AgBF_4$ procedure [11a, b].)

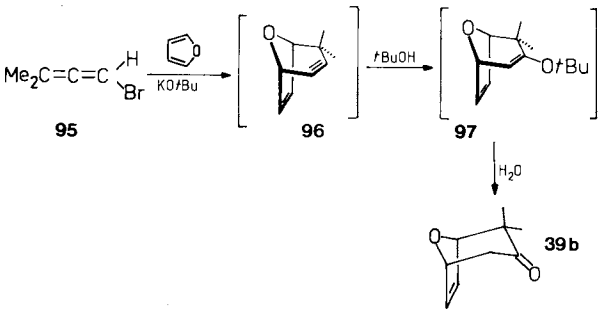


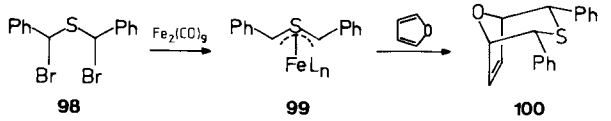
Bicyclic aminals are preparatively useful because they can be purified and stored more readily than the sensitive α-chloroenamines[11a, b].

2.6. Miscellaneous Reactions

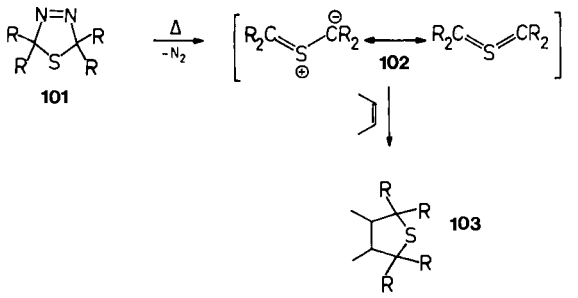
Allenic carbene **94** is isoelectronic with its protonated form **17b** ↔ **18b**, which in turn may be regarded as a didehydroallyl cation (Section 2.1). *Landor* et al.[41] have shown that dehydrobromination of **95** in the presence of furan affords a bicyclic ketone **39b** in 9% yield. Strained alkyne **96** has been postulated as an intermediate, which in the presence of *t*-butyl alcohol is thought to proceed to enol ether **97** and then to a ketone. Another reaction of theoretical interest is the dehalogenation of bis(α-bromobenzyl) sulfide **98** with $Fe_2(CO)_9$ in the presence of furan, affording **100**[42]. As an intermediate, the iron-stabilized sulfur ylide **99** has been proposed. Note that an uncomplexed sulfur ylide **102**, which may be generated by pyrolysis of a 2,5-di-



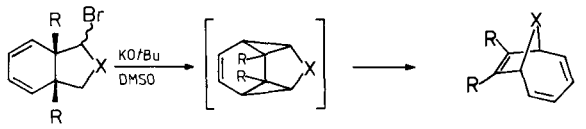




hydro-1,3,4-thiadiazoline **101**, functions as a 1,3-dipole or heteroallyl anion and hence can be trapped by olefins



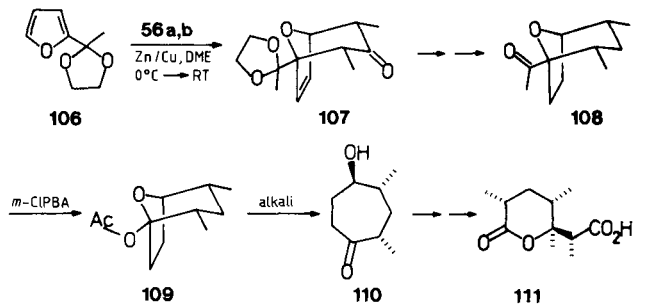
(**102** → **103**) in a 1,3-dipolar cycloaddition. *Hayami*'s work is an interesting example of an umpolung of a heteroallyl anion into a heteroallyl cation. If other 1,3-dipoles could be used in this fashion, seven-membered heterocycles would be accessible in addition to seven-membered carbocycles (cf. *e.g.* **39b**). An intramolecular variant which is possibly related to the reaction **98** → **100** (DMSO = dimethyl sulfoxide) is the base-induced rearrangement of **104** into **105**, studied by *Paquette*[43].



R = H, Me; X = CO, SO_2

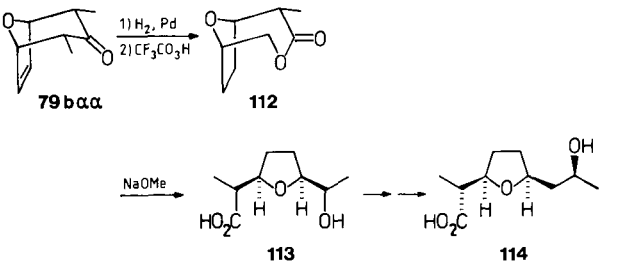
2.7. Further Applications in Synthesis

In dimethoxyethane (DME), ketalized 2-acetylfuran **106** readily affords adduct **107**, containing a bridgehead substituent. **107** has been transformed in several steps into the

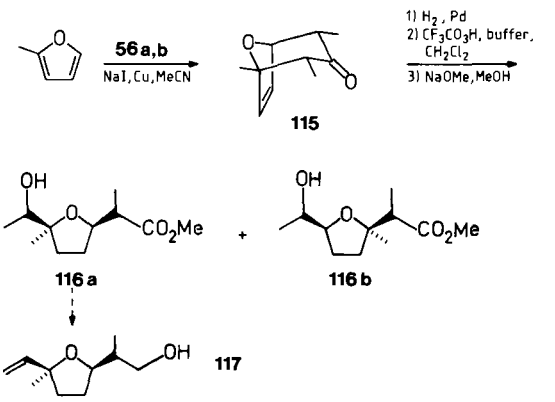


Scheme 9. Stereocontrolled synthesis of **107** and the Prelog-Djerassi lactone **111** [44].

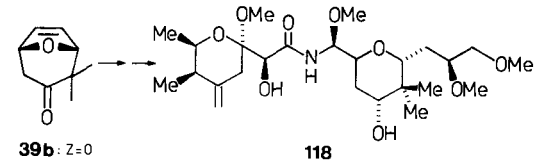
Prelog-Djerassi lactone **111** (Scheme 9)[44]. The sequence demonstrates how opening and removal of the ether bridge in **108** *via* Baeyer-Villiger rearrangement affords functionalized monocyclic cycloheptanes with defined stereochemistry. For entropy reasons it would be much more difficult or impossible to prepare a cycloheptane derivative such as **110** in a stereocontrolled fashion by reaction of an allyl cation with an open-chain diene. *White* et al.[45] have also used **79bαα**, which is simply **107** without a bridgehead substituent, to prepare nonactic acid **114**: Baeyer-Villiger oxidation of 8-oxabicyclo[3.2.1]octan-3-ones and opening of the resulting lactone **112** is clearly the method of choice for preparing *cis*-2,5-disubstituted tetrahydrofurans such



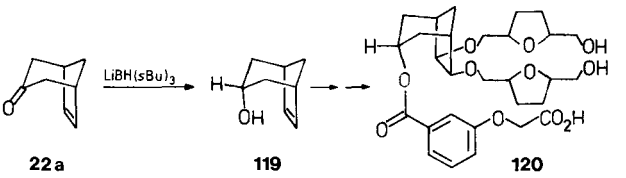
as **113**. We have used the same approach to prepare **116a** and its isomer **116b**; **116a** is a precursor for a stereoselective route to lilac alcohol **117**[46].



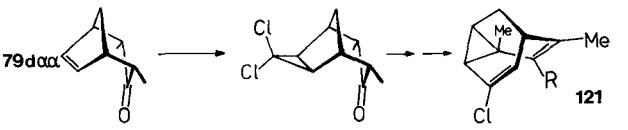
Another bicyclic ketone, namely **39b** (Z = O), has been used as starting material for a multistep synthesis of the "eastern half" of pederin **118**, which is the most complex,



known non-proteinaceous insect defensive compound[47]. The parent [3.2.1]bicycle **22a** has been elaborated in only a



few steps into the noncyclic ionophore **120**, which transports Ca^{2+} efficiently[48]; its 2,4-dimethylated homologue **79dαα** has been used by us as starting material to prepare functionalized barbaralanes **121** (Scheme 10)[49]. The two



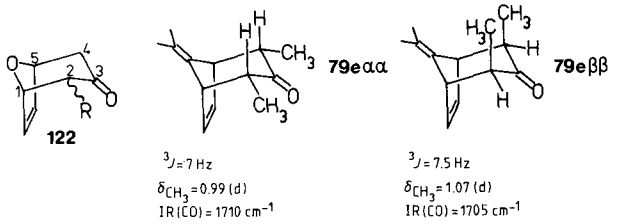
Scheme 10.

methyl groups in **121** serve as convenient "flags" in the ^{1}H-NMR spectra for determining the barrier of the degenerate Cope rearrangement.

3. Structural and Spectroscopic Properties of Bicyclo[3.2.1]oct-6-en-3-ones

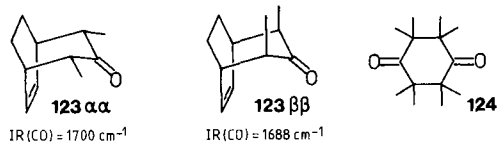
3.1. Flattening of Six-Membered Rings

The configuration of 8-oxabicyclo[3.2.1]oct-6-en-3-ones **122** which are monosubstituted at C-2 (and C-4) can readily be deduced from the coupling constants $^3J_{1,2}$. For *exo* 2-H (or 4-H), $^3J = 4.5-5$ Hz; for an *endo*, $^3J < 1.5$ Hz.



Interestingly, in **79eαα** and **79eββ**, the magnitude of the ^3J coupling constant of the methyl protons is slightly different, depending on whether the methyl groups are present in an α-configuration ($^3J = 7$ Hz) or β-configuration ($^3J = 7.5$ Hz)[32]. The smaller IR carbonyl frequency in **79eββ** can be attributed to partial flattening of the six-membered ring due to *syn*-diaxial Me···Me repulsion.

The sensitivity of the IR carbonyl frequency to conformational changes is also evident in **123ββ**[50]. **123ββ** has the flatter cycloheptanone moiety and hence smaller carbonyl frequency than epimeric **123αα**. The highly crowded,



bridged anthracene adduct **60c** adopts an almost C_{2v} conformation in the crystal: the five contiguous carbon atoms originating from the 2-oxopropanediyl bridge and the two quaternary bridgehead carbons are almost coplanar! A slight pyramidalization of the carbonyl group has also

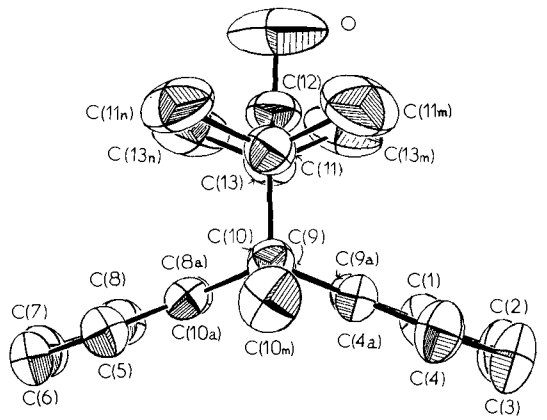


Fig. 1. Structure of **60c** in the crystal; view along the two planes of the benzene rings.

been detected (Fig. 1)[51]. 2,2,3,3,5,5,6,6-Octamethylcyclohexane-1,4-dione **124** also adopts a very flat C_{2v} chair conformation, as can be seen more clearly in the Newman projection (Fig. 2)[52].

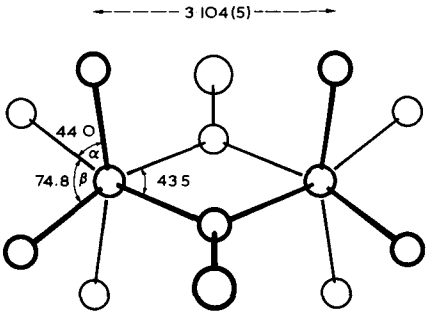
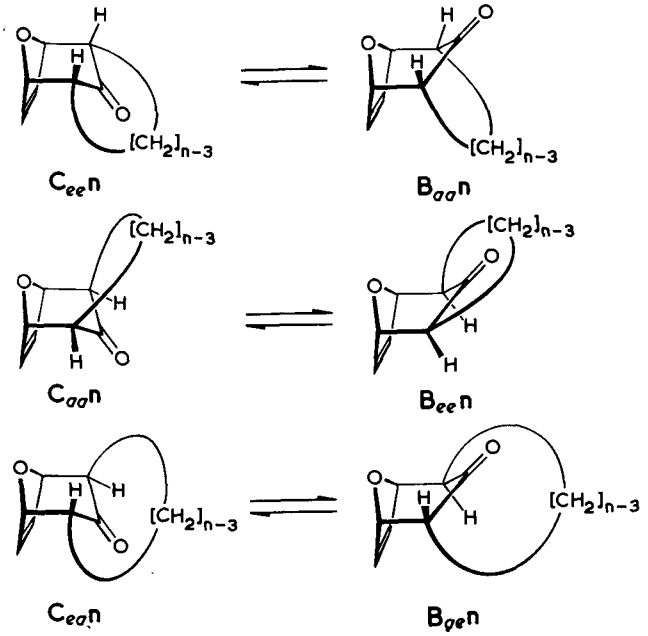


Fig. 2. Newman projection of **124**.

3.2. Conformational Mobility of Six-Membered Rings

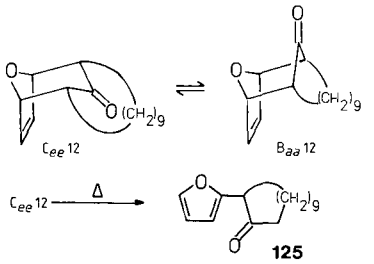
The effect of the methylene chain $(CH_2)_{n-3}$ on the shape of the six-membered tetrahydropyranone moiety can be seen in 2,4-bridged 8-oxabicyclo[3.2.1]oct-6-en-3-ones. A priori, the six-membered ring may be present in a chair conformation C and in a boat conformation B. Depending on the number (n − 3) of methylene groups, the six-membered ring can be deformed in almost predictable fashion. If the methylene chain is long enough (n ≧ 12), it may be attached *cis*-diequatorially (*ee*), *cis*-diaxially (*aa*) and equatorially-axially (*ea*), to either chair C or boat B. Accordingly, we have designated the various stereoisomers and their conformational relationship by simple, self-evident nomenclature (Scheme 11)[53].



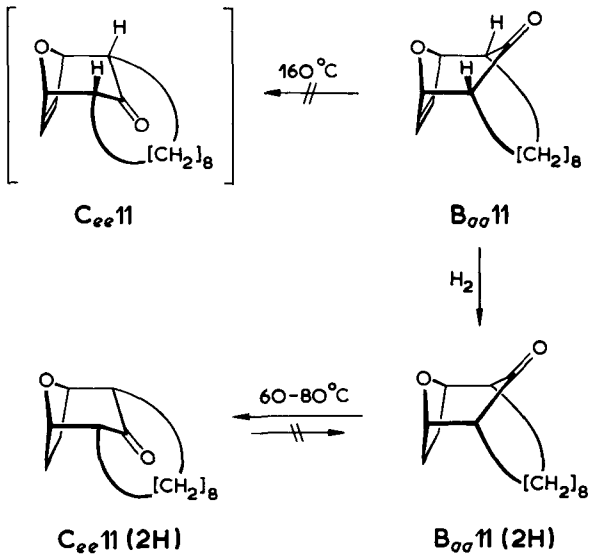
Scheme 11. Nomenclature for conformationally mobile tricycles.

A complete line-shape analysis has demonstrated the dynamic equilibrium $C_{ee}12 \rightleftharpoons B_{aa}12$. In CCl_4, $\Delta G^{+} = 16.0$ kcal/mol and $\Delta S^{+} = 1.5$ cal K^{-1} mol^{-1}, whereas in more polar solvents the more polar $B_{aa}12$ is favored progressively; in fact, the equilibrium $C_{ee}12 \rightleftharpoons B_{aa}12$ can be used as a

criterion for solvent polarity. The existence of $B_{aa}12$ can be ascribed to relief of nonbonding repulsion in $C_{ee}12$, *i.e.* the six-membered ring in $C_{ee}12$ is forced into a strained conformation by the methylene loop, and the carbonyl group is buried below the loop. The strain in $C_{ee}12$ has a chemical consequence, also: on being heated at 70°C, especially under the influence of acid, $C_{ee}12$ fragments to **125**, the product of a class C reaction. In contrast, the epimeric $C_{aa}12$ is comparatively stable under these conditions.

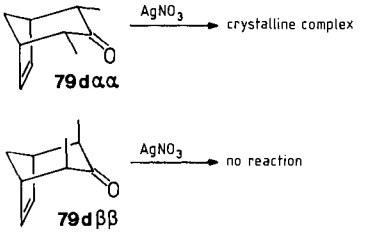


Predictably, the barrier to interconversion of the next higher homologue $C_{ee}13 \rightleftharpoons B_{aa}13$ is substantially lower ($\Delta G^{+} < 9$ kcal/mol), and there is a greater bias towards population of $C_{ee}13$. In contrast, $B_{aa}11$, which has a tighter methylene bridge than $B_{aa}12$, exists as a stable boat and does not show any tendency to spill over into chair $C_{ee}11$ on being heated to 160°C. After hydrogenation of the CC double bond, the crowded $B_{aa}11(2H)$ is isolated; however, on being heated to 60–80°C it is cleanly converted into the more stable chair rotamer $C_{ee}11(2H)$ ($E_a = 26.8 \pm 0.5$ kcal/mol, $\log A = 13.6 \pm 0.1$). A kinetic barrier of this magnitude allows us to describe $B_{aa}11(2H)$ and $C_{ee}11(2H)$ as discrete boat and chair atropisomers, *i.e.* in this case we may isolate two compounds which differ only in the conformation of the six-membered ring (Scheme 12). Hydrogenation of conformationally dynamic $C_{ee}12$ yields conformationally static $C_{ee}12(2H)$, but no $B_{aa}12(2H)$[53].

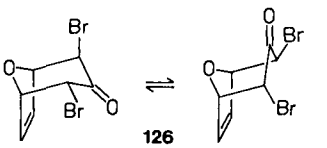


Scheme 12. Boat and chair atropisomers in bridged six-membered rings.

What is the reason for the special conformational behavior of these tricycles? The presence of the unsaturated bridge flattens the six-membered ring and causes concomitant strain in $C_{ee}12$, and more so in $C_{ee}11$. Conversion of the etheno into the ethano bridge lengthens the 2C bridge, and the previously deformed six-membered ring relaxes into a better developed chair.



Half-sided flattening of the six-membered ring by the etheno bridge shows up in another unexpected way: of the epimeric pair **79daα** and **79dββ**, the latter is thermodynamically less stable because of *syn*-diaxial repulsion of methyl groups. The mixture of the two isomers can be separated by treatment with aqueous silver nitrate, which selectively complexes the CC double bond of the thermodynamically *more stable* **79daα**. Presumably, silver nitrate complexation of the ββ-epimer is unfavorable because concomitant lengthening of the CC double bond—similar to hydrogenation of the tricycles—would destabilize it further by increasing *syn*-diaxial repulsion of the methyl groups[20,32].



Finally, **126** has been reported to show two IR carbonyl bands at 1734 and 1747 cm^{-1}[54] ($CHCl_3$). A dynamic equilibrium between chair and boat forms provides a possible rationale.

4. Electrophilic Intermediates and Reaction Mechanisms

4.1. The Nucleophilic Anchor Y

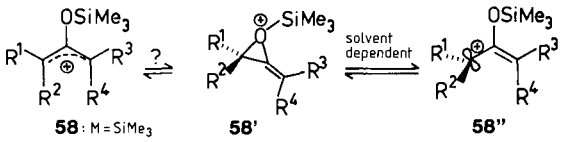
The stabilization of intermediate metal enolates as well as allyl cations by terminal alkyl groups and also by chlorine and bromine atoms (cf. reactions of polyhaloketones) needs no further comment. The exceptional position of 2-alkoxyallyl cations, *e.g.* derived from 2-methoxyallyl bromide, has also been stressed. The yield and type of product are also influenced profoundly by the group Y attached to the central carbon of the allyl system. What is the effect of Y on the structure of the allyl cation? How early or how late does Y intervene as a nucleophile? In the following, a few pertinent examples of groups Y will be discussed.

4.1.1. Oxygen as Heteroatom (Y= OM, OR); Allylic Resonance versus Oxygen Participation

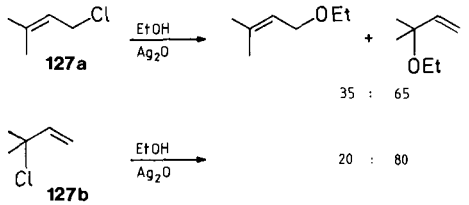
Although we have formulated oxyallyl cations as planar and delocalized (cf. **2**), rotation and a valence tautomeric change to perpendicular **2a** cannot easily be discounted. In fact, two special features of 2-oxidoallyl cations are

consistent with the existence of some oxygen participation in favorable cases.

Resistance to Elimination of Highly Alkylated Metal Oxyallyl Cations: Highly alkylated, conventional allyl cations enter easily into E1-like reactions to form dienes. For example, if the elimination product **42** from **41** is to be avoided, a low temperature and the absence of hindered tertiary amine are required[23] (cf. also conversion of **45** into **46**). In contrast, no significant elimination has been encountered with the 2-ethoxyallylic precursor **38** in the presence of amine under the same conditions[21] nor with permethylated metal oxyallyl cations at higher temperature. Thus, the reaction with anthracene to give **59c** and **60c** gave good yields in refluxing benzene (b.p. 81 °C)! We suggest that an E1 reaction—proton loss under neutral or acidic conditions—of conventional allyl cations is favored by uncoupling the π allyl overlap; in this way the proton to be lost becomes more acidic (see also formation of **143** from **139c** in Section 4.1.4). Such an intended elimination is prevented in metal oxyallyl cations such as **58**, M = $SiMe_3$, because on rotation the positive charge is partially anchored at oxygen as in **58'** and **58''**: **58'** is a valence tautomer and **58''** a rotamer.

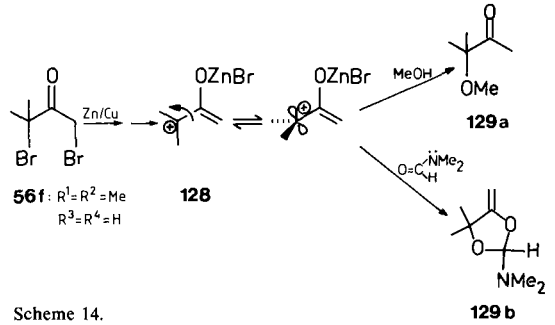


Regioselectivity of Metal Oxyallyl Cation Capture: Generally, solvolysis of unsymmetrically substituted allylic halides, even under S_N1 conditions, affords two regio-isomers. For example, the isomeric precursors **127a** and **127b** give different ratios of product (Scheme 13). The so-called



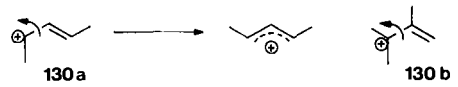
Scheme 13. Regioselectivity of capture of conventional allyl cations under S_N1-like conditions.

product spread, amounting to 15% in this example, is characteristic for conventional allylic halides and is inconsistent with a common intermediate in both reactions[55]. In contrast, the reaction of metal oxyallyl cations with nucleophiles in polar solvents is regioselective; for example,



Scheme 14.

only the more stable tertiary terminus in **128** is uncoupled in methanol[56a] (cf. formation of **129a**) and in *N,N*-dimethylformamide [cf. **129b**, the formation of which involves initial attack by the nucleophilic oxygen of dimethylformamide (DMF)] (Scheme 14)[56b]. Is the postulated perpendicular metal oxyallyl species just a rotamer with a long carbon-oxygen bond (*e.g.* **58''**) or is it a discrete methyleneoxiranium ion (*e.g.* **58'**)? Necessarily, uncoupling of π allyl overlap depends on several factors including temperature, electron demand of the metal, solvent polarity, and substitution pattern. The rotational barrier in **130a** (24

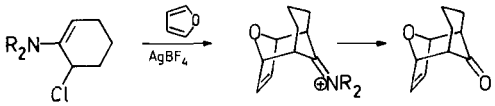


kcal/mol)[57a] and the much lower barrier in **130b** (12.9 kcal/mol)[57b], which contains a tertiary terminus, should be borne in mind. In fact, ion **128**, which is related to ion **130b**, appears to be one of the best candidates for oxygen participation at present[57c].

4.1.2. Nitrogen as Heteroatom (Y = NR_2)

In the series of chloroenamines **10** the nucleophilic center is nitrogen (Y = NR_2), and only the alkyl groups attached to nitrogen vary. Nonetheless, as shown by *Schmid*[11a,b] the yield of furan adduct **132** changes, being highest (68%) for α-chloropyrrolidineenamine **10a**, which works much better than acyclic dimethylaminoenamine **10b**, morpholinoenamine **10c**, and piperidinoenamine **10d** (Table 5). The decreasing yield along this series parallels

Table 5. Cycloadducts **132** by reaction of 2-amino-3-chlorocyclohexenes **10** and furan in the presence of $AgBF_4$ [11a, b].

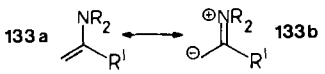


R_2N		$\delta(^1H)$ [a]	**132**, Yield [%]	Ref.
10a		4.4	68	[58a]
10b	Me_2N	ca. 4.5	37	[58b]
10c		4.65	23	[58a]
10d		4.7	20	[58a]

[a] ^{1}H-NMR signal of the olefinic protons.

the ratio of *C*-alkylation/*N*-alkylation of the corresponding enamines (without chlorine) and reflects:

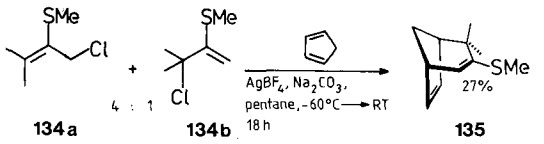
1) the well-known reactivity of enamines toward electrophiles,
2) the ^{1}H-NMR chemical shift of the terminal olefinic protons, and
3) the ^{13}C-NMR chemical shift of the olefinic carbons.



In other words, p,π overlap and carbon nucleophilicity—represented by dipolar form **133b**—drop along this series. Again, the question—early or late intervention of the nucleophilic group NR_2—cannot be answered definitively. Clearly, nucleophilic participation of $Y=NR_2$ depends not only on substituents R, but also on ring size n: it is more favorable for n=6 than for n=5, because strain in the corresponding ammonium ion **92** is smaller.

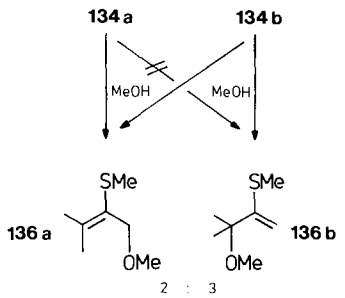
4.1.3. Sulfur as Heteroatom (Y=SR)

From the point of view of synthesizing seven-membered carbocycles, 2-methylthioallylic halides are not promising. By analogy to **40a**, **134a,b** is readily accessible and affords **135**[59], but the yield (27%) is not much better than

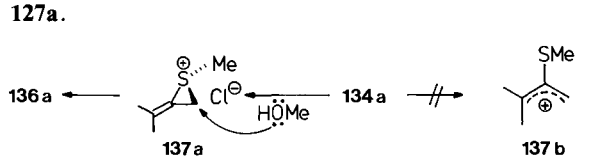


the total yield for the reaction of structurally related **35a** with cyclopentadiene. With furan, **134** affords products of class C only, analogous to the formation of **48a,b** from **47**.

Nonetheless, as *Schöllkopf* and *Riefling*[59] have shown, 2-alkylthioallyl halides are of mechanistic interest since the highly nucleophilic sulfur is able to participate in 1,3-interactions (cf. **2a**). Methanolysis of the primary chloride **134a**

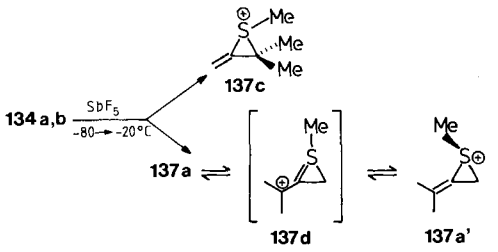


produces the primary ether **136a** regiospecifically, whereas the tertiary chloride **134b** furnishes primary and tertiary ethers in a ratio of 2:3. If methanolysis were to yield planar and delocalized allyl cation **137b** directly, we would expect tertiary **134b** to react about three times faster than its primary isomer **134a**, by analogy to **127b** and **127a**.



In fact, the converse applies: the primary chloride **134a** is solvolyzed about ten times *faster* than tertiary **134b**. Control experiments in the presence of sodium methoxide suggest that it is unlikely that methanolysis of **134a** and **134b** is an S_N2 reaction. Instead, sulfur participation with generation of the methylenethiiranium ion **137a** provides a simple explanation for the enhanced rate of **134a** and regiospecific formation of **136a**. The solvolysis of the tertiary chloride **134b** is more complex mechanistically since **134b** may ionize, at least in part, without participation of sulfur to give the observed mixture of isomeric allyl ethers **136a** and **136b**. Hence, allyl cation **128** and the cations derived from **127a** and **127b** as well as from **134a** and **134b** are all subtly different, although they all have the same basic isoprenoid carbon skeleton.

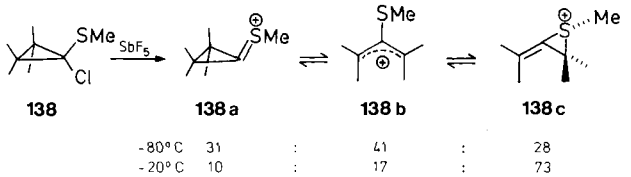
Schöllkopf and *Riefling*[59] have also investigated the ionization of **134a** + **134b** in SbF_5 from −80 to −20°C by ^{1}H-NMR spectroscopy and concluded that two isomeric allene-episulfonium ions **137a** and **137c** are present. The



temperature-dependent ^{1}H-NMR spectrum of **137a** suggests the possibility of a facile inversion at the pyramidal sulfur atom.

The barrier to inversion has been estimated to be *ca.* 8—10 kcal/mol[59], which is *ca.* 16 kcal/mol lower than the normal barriers to inversion of sulfonium sulfur[60]. Inversion appears to be coupled with *E/Z* exchange of the terminal methyl groups. An effective interaction of a vacant d-orbital on sulfur with the olefinic π system probably requires that the sulfonium sulfur attain trigonal planar geometry (cf. **137d**). Again, the planar delocalized allyl cation **137b** is not detectable under these conditions[59].

Finally, the temperature-dependent ^{1}H-NMR spectrum of the cations produced by ionization of **138** (Scheme 15) suggests that all three valence tautomers **138a-c** are present. With increasing temperature **138c** increases at the ex-



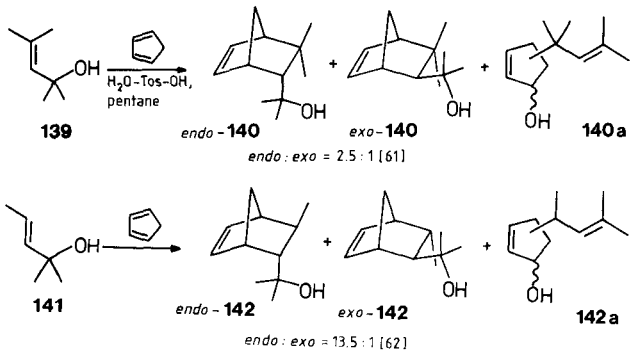
Scheme 15. Ratio of valence tautomers from ionization of **138** at −80°C and at −20°C.

pense of **138a** and **138b** (**138a** → **138b** → **138c**). On the basis of its NMR spectrum, the thiocyclopropyl cation **138a** has been proposed to be *pyramidal* rather than planar at the carbenium center; in this way, $2sp^x$-3p(S) overlap is maximized, with little if any $2sp^x$-2p(S) overlap, which is antibonding[59]. Finally, whereas we have discussed the stabilization of positive charge by 1,3-interactions, the possibility of stabilization by 1,5-interactions has hardly been exploited (cf. **76**).

4.1.4. Allyl Cations as Dienophiles in Diels-Alder Reactions

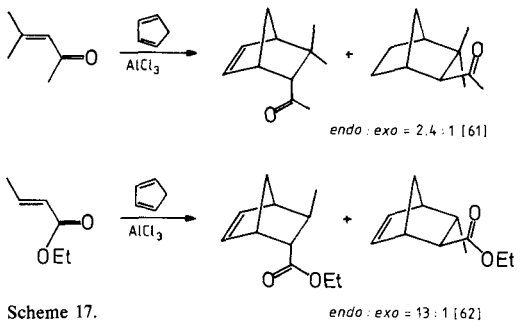
Having dealt with allyl cations containing a very nucleophilic group (Y=SMe), we now turn to the case Y=H.

Clearly, formation of seven-membered rings on reaction with 1,3-dienes is now unfavorable, the hypothetical product being a secondary cation. Instead, the two-phase reaction of allyl alcohols **139** and **141** furnishes six-membered rings, *i.e.* norbornenylmethanols **140**[61] and **142**[62] in addition to **140a** and **142a**, respectively (Scheme 16). Detailed mechanistic investigations suggest that cycloadducts **140** and **142** are formed via stepwise, pull-push Diels-Alder reactions. A stepwise process is also reasonable, because the central carbon atom of a planar allyl cation contains a node in the LUMO, so that there should be no initial bonding to this atom. Interestingly, compounds of type **140a** and **142a**—which are virtually unknown in conventional Diels-Alder additions to cyclopentadiene—correspond to products of class C in the synthesis of seven-membered carbocycles from allyl cations and 1,3-dienes (see *e.g.* Scheme 3).

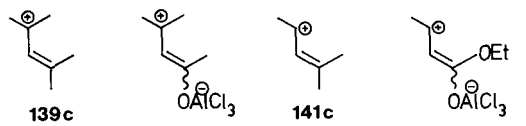


Scheme 16.

The $AlCl_3$-catalyzed Diels-Alder reaction of mesityl oxide or crotonic ester to cyclopentadiene yields *endo/exo* adducts in the ratio 2.4:1 and 13:1, respectively (Scheme 17). Since similar key cationic intermediates (cf. Scheme 18) can be formulated for the reactions in Schemes 16 and 17, and the *endo* selectivity of both sets of dienophiles is almost identical, we have concluded that the two $AlCl_3$-catalyzed Diels-Alder reactions are also stepwise, pull-push processes[61,62].

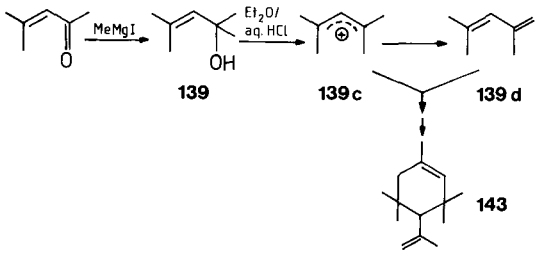


Scheme 17.



Scheme 18.

In the absence of cyclopentadiene, allyl alcohol **139** has been cyclized to tetramethyllimonene **143**, which, starting from mesityl oxide, can be prepared in quantities of at least 60 g per batch (Scheme 19). Although **143** may be regarded formally as the Diels-Alder dimer of 2,4-dimethyl-1,3-pentadiene **139d**, it is, in fact, formed by combination of **139c** and **139d** in a multistep reaction which resembles the biosynthesis of parent limonene[63]. The tetramethylallyl cation **139c**—which must be nonplanar because of steric repulsion of the two *Z*-methyl groups—is readily deprotonated to diene **139d**, *unlike* structurally related metal oxyallyl cations (see, *e.g.* **58**, $M=SiMe_3$; $R^1=R^2=R^3=R^4=Me$ and Section 4.1.1) which have been generated and captured by anthracenes to give **59c** and **60c** at temperatures as high as 80°C.



Scheme 19. Biomimetic one-pot preparation of **143** from mesityl oxide.

4.2. Guidelines for Reactions of Allyl Cations and 1,3-Dienes

Currently known experimental facts and the mechanistic discussion to follow are summarized in the following.

1. Furan, more than cyclopentadiene, favors the compact mode of cycloaddition[5].
2. The electrophilicity of oxyallyl intermediates decreases along the series iron oxyallyl > siloxyallyl > zinc oxyallyl $\gtrsim$ lithium oxyallyl > sodium oxyallyl > cyclopropanone ("oxidoallyl").
3. For reactions within class A and reactions near the A/B border, the more electrophilic allyl cation intermediate has the greater propensity toward extended attack of the diene[5].
4. With increasing electrophilicity of the allyl cation, class B and finally class C reactions are promoted. Conversely, decreasing electrophilicity of the allyl cation requires increasing nucleophilicity of the diene for a class A and class B cycloaddition to occur. Nonplanar allyl cations with poor orbital connectivity must react via classes B and C.
5. A reaction of a structurally defined cation belongs at most to two classes, *i.e.* classes A and B or classes B and C. Thus, formation of class C products precludes class A as a source of cycloadducts and conversely, operation of a class A reaction makes it unlikely that products of class C are formed[*].

4.3. Stereochemistry and Product Type; Criteria and Assignment of Classes A, B, and C

4.3.1. Compact versus Extended Transition States; Class A Requirements

Reaction of 2,4-dibromo-3-pentanone **56a,b** with cyclopentadiene in the presence of three different reducing

[*] This postulate may also be useful for locating Diels-Alder reactions which proceed stepwise; cf. formation of **140a** and **142a**.

agents and under quite different experimental conditions (Table 6) is stereoselective: only *ee*-adducts **79dαα** and *aa*-

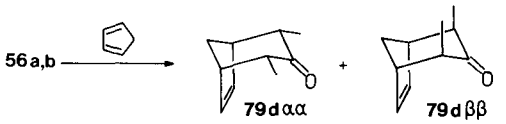


Table 6. Ratios of compact to extended transition states (αα : ββ) in the cycloaddition of cyclopentadiene to 2,4-dibromo-3-pentanone **56a,b** *via* various oxyallyl intermediates.

Method	αα : ββ	Ref.
NaI/Cu, MeCN	6.4 : 1	[32]
2-Bromo-3-pentanone instead of **56a,b**; $LiClO_4$, NEt_3	1.9 : 1	[64b]
Zn/Cu, DME, 0–25 °C	1.7 : 1	[32]
$Fe_2(CO)_9$, C_6H_6	0.89 : 1	[64a]

adducts **79dββ** are formed. There is no leakage into the *ea*-epimer **79aβ**. The $Fe_2(CO)_9$ induced reaction of **56g** ($R^1 = R^3 = i$Pr; $R^2 = R^4 = H$) proceeds analogously, giving *ee*- and *aa*-adducts only, in a ratio 1 : 1[64]. Even the reaction of tetrabromoacetone **56d** with cyclopentadiene via the $(EtO)_3B$/Zn procedure affords *ee*-adduct **70** and *aa*-adduct **71**, but no *ea*-adduct **72**[16b]. These experimental findings are all the more striking when compared with the furan cycloadditions in Section 4.3.2, and they suggest simultaneously that

a) W-configurated allyl cations **58** ($R^1 = R^3 = H$) are generated stereoselectively as the only significant species and
b) these ions are captured by cyclopentadiene via compact and extended transition states[5] in a class A reaction.

In other words, the *ee* : *aa* ratio is identical to the steric course of attack, *i.e.* compact versus extended. Invoking the principle that the more electrophilic allyl cation has the greater propensity toward extended attack (Section 4.2), we conclude that sodium oxyallyl is the weakest electrophile and iron oxyallyl the strongest (Section 4.2). On the basis of this theory, any oxyallyl cation which gives a compact : extended ratio smaller than 0.89 : 1 in the reaction with cyclopentadiene must be considered to be more electrophilic than iron oxyallyl.

4.3.2. Loss of Allyl Cation Configuration; Sufficient Criterion for Class B

In the presence of furan, dehalogenation of **56a,b** with three different reducing agents affords all three epimeric cycloadducts: **79bαα**, **79bββ**, and **79bαβ** in varying amounts (Table 7). The marked loss of allyl cation configuration (21.3% αβ adduct) in the reaction with 3,4-dimethylfuran should also be noted. Leakage into α,β epimeric cycloadducts has been found inter alia for reactions of **56a,b** with *N*-methoxycarbonylpyrrole[64] and with 6-acetoxyfulvene[32] using $Fe_2(CO)_9$ and NaI/Cu, respectively. We have suggested that W-configurated allyl cations are generated initially, but that they partially lose their configuration once an intermediate of type **4** has been generated: attack

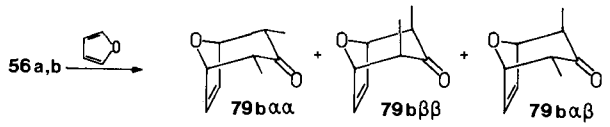
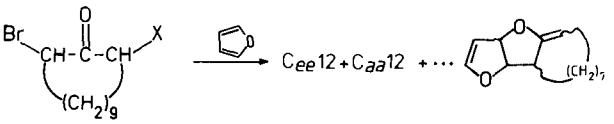


Table 7. Epimer ratios in the cycloaddition of furan and 3,4-dimethylfuran to 2,4-dibromo-3-pentanone **56a,b** in the presence reducing agents.

Reducing-agent	Solvent	Epimer ratios αα	ββ	αβ
NaI/Cu	MeCN	90.9	3.0	6.1
Zn/Cu	DME	73.9	8.7	17.4
	MeCN	74.5	10.3	15.2
$Fe_2(CO)_9$	without	44	—	56 [64a]
		(59.7	3.8	36.5) [a]
Zn/Cu	DME	(45	33.7	21.3) [b]

[a] Base catalyzed equilibration. [b] Adducts to 3,4-dimethylfuran.

at either face of the enolate π system in **4** is possible, giving all three epimeric adducts in step 2).



144a: X = Br
144b: X = H
144c

Table 8. Cycloaddition of furan to α-bromocyclododecanone **144** to afford $C_{ee}12$, $C_{aa}12$, and other products as a function of different oxallyl intermediates. **144c** is formed by the reaction with NaI/Cu. $C_{ee}12 : C_{aa}12$ indicates the ratio of compact to extended transition state.

Reagent	Yield [%] $C_{ee}12$	$C_{aa}12$	$C_{ee}12 : C_{aa}12$	$C_{ae}12$	Other products [a]	Ref.
144a, $Fe_2(CO)_9$	—	7	[c]	45	34	[64a]
144, Zn/Cu on Al_2O_3 columns	6 [b]	1 [b]	6 : 1	1 [b]	0.5 [b]	[53]
144a, NaI/g or NaI/Cu, MeCN	54	6	9 : 1		**144c**	[65]
144b, base	53.9	4.1	93 : 7			[37]

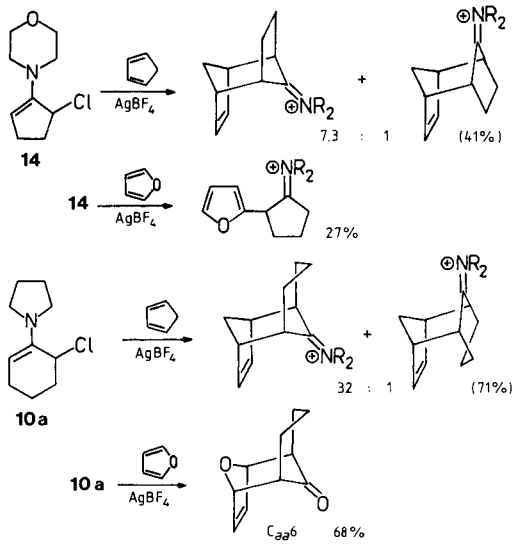
[a] 2-(2-Furyl)cyclododecanone. [b] The numbers are product ratios and not absolute yields. [c] Extended transition state.

The preparation of the conformationally dynamic tricycle $C_{ee}12$ (see Section 3.2) by three different routes is also instructive (Table 8): zinc oxyallyl furnishes $C_{ee}12$ (presumably via a W-configurated allyl cation and a compact transition state) as a major product in addition to $C_{aa}12$ (which probably arises via an extended transition state giving $[B_{ee}12] \rightarrow C_{aa}12$) in a ratio 6 : 1. There is also leakage into $C_{ae}12$ and products of class C. Less electrophilic sodium oxyallyl is more selective (compact : extended = 9 : 1), and the base catalyzed reaction of α-bromocyclododecanone with furan is similar. Thus, the reactivity-stereoselectivity relationship (Section 4.2) holds, although at least some reactions belong without doubt in class B.

On the other hand, the most electrophilic species, *i.e.* iron oxyallyl from the Noyori reaction, does not give any $C_{ee}12$, but mainly $C_{ae}12$ (45%) and some $C_{aa}12$; products of class C are now more prominent than in any of the other procedures (cf. Section 4.2).

A beautiful example linking stereochemistry and product type with electrophilicity of the allyl cation has been

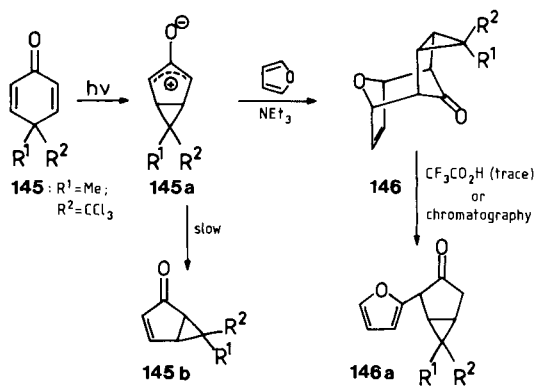
uncovered by *Schmid*[11a,b] in the reaction of cyclic 2-aminoallyl cations with cyclopentadiene and furan (Scheme



Scheme 20. Products of the reaction of 2-aminocyclopentenyl and 2-aminocyclohexenyl cations with cyclopentadiene and furan [11a, b]. Compound **14** was prepared in 80% purity and used further. With cyclohexadiene instead of cyclopentadiene, **14** forms the two stereoisomeric adducts in *ca.* 30% yield: *C. Ganter*, personal communication; see also Scheme 2.

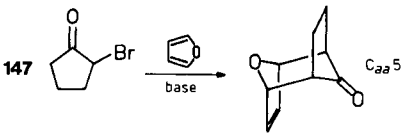
20). As expected, furan favors the compact mode of cycloaddition vis-à-vis cyclopentadiene (Section 4.2). On the basis of the reactivity-stereoselectivity relationship (Section 4.2), the morpholinocyclopentenyl cation derived from **14** (compact : extended = 7.3 : 1) is more electrophilic than the pyrrolidinocyclohexenyl cation derived from **10a** (compact : extended = 32 : 1). It is pleasing to note that this conclusion is consistent with the type of product formed from the corresponding reactions with furan: whereas the more electrophilic cyclopentenyl species affords product of class C, the less electrophilic cyclohexenyl species affords product of class B (or even class A), *i.e.* the compact adduct $C_{aa}6$ (the extended isomer is not detectable).

From a preparative viewpoint it is noticeable that the cation from **14**, *i.e.* the five-membered ring derivative, reacts only reluctantly with cyclopentadiene (41% yield) and also with furan (27% yield, only class C; see also formation of **65**). Irradiation of cross-conjugated dienone **145** generates

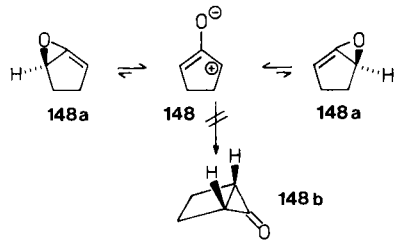


the familiar type of zwitterion **145a**, which is a substituted cyclopentenyl cation. Thanks to the presence of the trichloromethyl group ($R^2 = CCl_3$), the cyclopropane "walk" (**145a** → **145b**) is now a slow process. In the presence of furan and triethylamine, *Samuel* has isolated the highly strained adduct **146**, which is easily transformed into products of class C, *i.e.* **146a**[66].

Although parent $C_{aa}5$ itself can apparently not be made from **14** via the silver salt route (Scheme 20), it has been obtained more recently under basic conditions, *i.e.* by



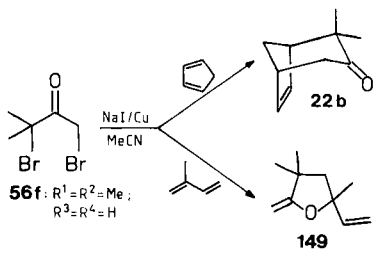
treatment of **147** with base in the presence of furan[37]. Clearly, the 2-oxidocyclopentenyl cation **148** is a special oxyallyl system; because of the high strain energy, the formation of bicyclo[2.1.0]pentan-5-one **148b** from planar **148**



is impossible (note also that polycyclic α-halocyclopentanones derived from **147** undergo base catalyzed Favorsky-type ring contraction only *via* the semibenzilic route, and not via fused cyclopropanones of type **148b**[67]). Since the generation of folded valence tautomer(s) **148a** from **148** also seems difficult, charge separation is structurally enforced: **148** and the cation derived from 2-aminocyclopentenyl chloride **14** should be comparatively electrophilic.

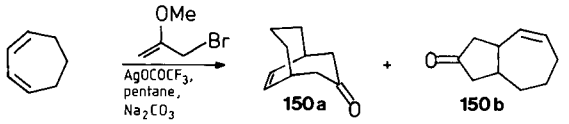
4.3.3. Electrophilic Substitution and Electrophilic Addition with Formation of Five-Membered Carbocycles and Heterocycles; Class C Reactions

The facilitation of electrophilic substitution by an increase in electrophilicity of the allyl cation (Section 4.2) needs no further comment. Likewise, the possibility of forming class C products by fragmentation of class B cycloadducts, especially by Lewis acid catalysis and at higher temperature, has been exemplified several times (*e.g.*, **146** → **146a**, **5** → **6**). Indeed, the formation of products of class C has been used throughout this article to assign class B to any concurrent cycloadditions which afford seven-membered rings (Section 4.2). Conformational factors are often responsible for a change of mechanism: Whereas reaction of **56f** with NaI/Cu and cyclopentadiene yields



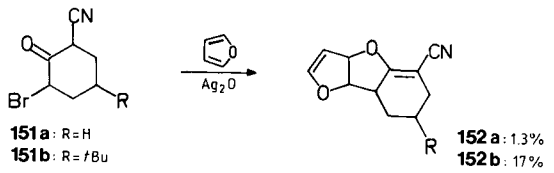
22b, reaction with isoprene affords sensitive α-methylenetetrahydrofurans, **149** being the major regioisomer (class C)[68]. The 2-alkylidenetetrahydrofuran moiety (cf. **149**,

152, and Table 6) occurs in prostacyclins, which show remarkable biological activities[69].—In contrast to the reaction of **56f** with NaI/Cu, the dehalogenation with Zn/Cu furnishes seven-membered and five-membered carbocycles[16a, 70].

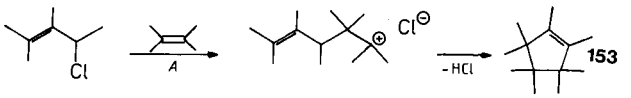


The conformationally flexible cyclohepta-1,3-diene and 2-methoxyallyl bromide yield **150a** (class B), which is a convenient precursor of the theoretically interesting manxane (bicyclo[3.3.3]undecane), as well as hexahydroazulen-2(1*H*)-one **150b** (class C) by the silver salt route[71]. More recently, we have annelated the conformationally rigid cyclopentadiene to a [3.3.0]bicycle (see **32** and analogous reaction from **35a**).

With certain oxyallyl systems, furan also participates in cycloadditions of class C (see also Table 8). In the presence of Ag_2O and furan, 3-bromo-2-oxocyclohexanecarbonitrile **151a** gives a trace of **152a**, whereas **151b** affords



the corresponding tricyclic **152b** in 17% yield[36]. Again, a slight geometric alteration of the σ framework has a pronounced effect on oxyallyl reactivity.



Scheme 21. *A:* $ZnCl_2 \cdot OEt_2$, CH_2Cl_2, −78°C/7.5 h; 25°C/0.5 h, in the presence of gaseous HCl.

Finally, allyl cations may also react with monoolefins. In this way permethylcyclopentene **153** has been prepared recently (Scheme 21)[72].

5. Conclusions

There now exist many procedures for generating and capturing allyl cations, but the question often asked—what is the best, quickest, safest, least expensive and least toxic method—is, in fact, wrongly posed. Instead, we must enquire more specifically: what is the best method for making a particular cyclic compound of interest? Once the structure of the π system and the substitution pattern of the allyl cation have been fixed, we must then decide how electrophilic the allylic component should be. Within these requirements, the silver salt route is especially useful for preparing seven-membered rings, because it allows the generation of highly electrophilic cations while at the same time tolerating nucleophilic groupings such as Y=OR and NR_2. Because of the crucial role played by Y, the reactions described are not only a challenge to preparative carbocation chemistry and to "aliphatic Friedel-Crafts chemistry", but also explose explore (Y=O⁻), metal enolate (Y=OM), enamine (Y=NR_2) and allylsilane chemistry (Y=CH_2SiMe_3), to list a few nucleophilic anchoring groups Y. Even seemingly trivial variations in the allyl cation substituents, including Y, may have a profound effect on the course of the reaction and the yield. Nor have all procedures yet been optimized. As I have tried to show, the formation of seven-membered rings is versatile and subtle from a mechanistic view: the reaction may take a concerted *and also* a stepwise course, depending on the factors discussed. In future, increased mechanistic understanding will stimulate new synthetic work and vice versa.

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Destabilized Carbocations

By Thomas T. Tidwell*

Carbocations are intrinsically reactive species, and in early studies of their generation and properties the more accessible with stabilizing influences were naturally the prime objects of interest. Now, however, it is possible to extend the scope of these studies to include factors which tend to destabilize carbocations. By using the carbocations $CH_3^{\oplus}$ and $C_2H_5^{\oplus}$ as reference ions, such destabilizing factors can be defined; these include various structural factors, antiaromaticity effects, and the presence of electron-withdrawing substituents. Such factors can be studied by their effect on the thermodynamics of carbocations, their effect on reactivities, and by the spectroscopic properties of long-lived carbocations. Destabilized carbocations of this type are receiving increasing attention and promise to remain an active subject of investigation.

1. Introduction

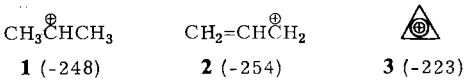
The half century from 1920 to 1970 saw the evolution of carbocations from species that were not considered to be of significance in organic chemistry to familiar intermediates that were routinely implicated in chemical processes and were included in all textbooks on the subject. At the beginning of this period, *Meerwein*[1] set off this development by reasoning that carbocations were involved in the rearrangement of camphene hydrochloride to isobornyl chloride, and were analogous to the long-lived ions formed from triphenylmethyl chloride. At the close of the half century, a five volume review of the field appeared[2] as well as a definitive review article by *Olah*[3] reporting the very extensive research, carried out primarily in his laboratory, on the generation of a diverse array of long-lived carbocations directly observable by spectral methods, most informatively by NMR. During this period the study of carbocations was one of the most actively pursued areas of research in organic chemistry, with a particular concentration of effort being directed to the study of the reaction steps and intermediates involved in solvolyses. As a result of this, the chemistry of carbocations, including their generation, properties, and reactions, progressed from an essentially unknown area to a mature science.

In the intervening decade there has been less emphasis on the study of carbocations, although very important developments have been made, including accurate delineation of the enthalpy of formation of carbocations using solution phase calorimetry[4], measurements of their gas-phase energetics[5], and theoretical investigations of many carbocations[6]. There has also been a significant increase in understanding solvolytic processes and the associated ionic and ion-pair intermediates involved[7,8].

With these accomplishments, it is now possible to consider the chemistry of carbocations as a unified whole[9], and it is the purpose of this review to examine one aspect of this area; namely, the factors which tend to *destabilize* these ions.

The simplest carbocations, consisting only of carbon and hydrogen, which have been directly observed in solution are the 2-propyl **1**[10], allyl **2**[11], and cyclopropenyl **3**[12] cations. These species have been characterized by their NMR spectra and heats of formation[5,13], and each may be considered to be stabilized relative to the ethyl cation using the hydride affinity of this species as a reference value (cf. (a)). The ΔH^0-values for **1**—**3** are given in parentheses, and the greater stability of these species may be attributed to the presence of an extra alkyl substituent, allylic resonance, and aromatic delocalization, respectively. These stabilizing effects are quite familiar, but only in recent years have destabilizing factors been considered systematically.

$$C_2H_5^{\oplus} + H^{\ominus} \longrightarrow C_2H_6\ ;\ \Delta H^{\circ} = -272\ \text{kcal/mol} \qquad \text{(a)}$$



1 (-248) **2** (-254) **3** (-223)

In this review $CH_5^{\oplus}$ and $C_2H_5^{\oplus}$ are considered as unstabilized species, and destabilized carbocations are defined as those with some structural feature that tends to reduce their thermodynamic stability relative to one of the unstabilized ions. In practice, unstabilized ions exist only transiently in solution, and hence almost all the examples of destabilized ions considered here have additional stabilizing influences to counteract the destabilizing effects.

2. Unstabilized Carbocations

An elegant technique which has been used for the study of bona fide free $CT_3^{\oplus}$ in solution is the decay of tritiated methane[14].

$$CT_4 \rightarrow CT_3^{\oplus} + {}^3He + \beta^{\ominus}$$

The course of electrophilic aromatic substitutions undergone by the tritiated methyl cations formed have been monitored by radiochemical techniques. These species, described as "the most powerful carbocations hitherto produced in solution"[14b], display remarkable selectivity.

There have been several studies in which evidence for generation of the relatively unstable $CH_3\overset{\oplus}{C}H_2$ species in solution have been obtained. Deamination of ethylamine labeled with ^{14}C proceeded via substitution accompanied

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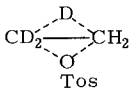
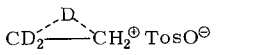
by only 1.5% rearrangement involving hydride migration[15], but solvolysis of CD_3CH_2OTos in FSO_3H gave partial deuterium scrambling without hydrogen exchange with the solvent[16]. This result appears to exclude an elimination-readdition mechanism (b) but does not differentiate between paths involving the ethyl cation (c) and a concerted rearrangement (d). The magnitudes of the observed

$$CD_3CH_2OTos \not\rightleftharpoons CD_2{=}CH_2 + TosOD \qquad (b)$$

$$CD_3CH_2OTos \longrightarrow CD_3CH_2^{\oplus}\ TosO^{\ominus} \longrightarrow {}^{\oplus}CD_2CH_2D\ TosO^{\ominus} \qquad (c)$$



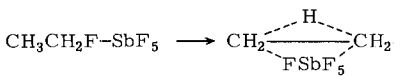
$$CD_3CH_2OTos \longrightarrow \quad \text{or} \quad \longrightarrow TosOCD_2CH_2D \qquad (d)$$



β-deuterium isotope effects on the rate of reaction have been interpreted as simultaneous rearrangement and ionization as shown in (d)[16c].

Olah et al.[17] studied CH_3CH_2F-SbF_5 complexes which undergo rapid intramolecular hydrogen and fluoride exchange with SbF_5 without intermolecular hydrogen exchange with the solvent DF or SO_3DF[17]. This was interpreted as requiring formation of a $C_2H_5^{\oplus}SbF_6^{\ominus}$ ion pair, although it does not appear that a concerted exchange can be excluded.

$$CH_3CH_2F{-}SbF_5 \rightleftharpoons CH_3CH_2^{\oplus}\ SbF_6^{\ominus}$$

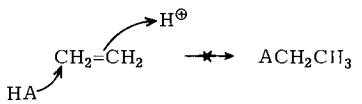


The reaction of HF-TaF_5 with $CH_2{=}CH_2$ and methane in a flow system was proposed to involve formation of ethyl cations which alkylated methane as shown in (e)[18a]. Formation of ethyl cations in solution by protonation of ethane in FSO_3H-SbF_5 or HF-SbF_5 according to (f) has also been proposed[18b].

$$CH_2{=}CH_2 + HF \xrightarrow[-F^{\ominus}]{} CH_3\overset{\oplus}{C}H_2 \xrightarrow[-H^{\oplus}]{CH_4} CH_3CH_2CH_3 \qquad (e)$$

$$CH_3CH_3 \xrightarrow{H^{\oplus}} CH_3\overset{\oplus}{C}H_2 + H_2 \qquad (f)$$

Kinetic evidence for the formation of ethyl cations by protonation of $CH_2{=}CH_2$ in H_2SO_4 was obtained in our laboratory[19]. In general, rates of alkene protonations correlate with substituent effects, and the measured reactivity of ethylene was somewhat less than that predicted by this correlation. This negative deviation emphasized the absence of any good stabilizing mechanism for the ethyl cation compared to more highly substituted carbocations. Intervention of a concerted addition of sulfuric acid to ethene as in (g), bridging, or some other mechanism bypassing formation of $CH_3CH_2^{\oplus}$ would be expected to result in a higher rate than predicted from the linear free energy correlation. The fact that the rates show a marked dependence on solvent acidity but not solvent nucleophilicity also argues against a concerted addition.



$$CH_2{=}CH_2 \not\longrightarrow ACH_2CH_3 \qquad (g)$$

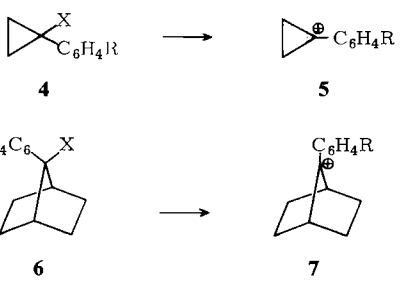
Considering the difficulty in obtaining conclusive evidence for the generation of $C_2H_5^{\oplus}$ in solution, it is not surprising that, except for the radiochemical method mentioned previously[14], evidence for the generation of $CH_3^{\oplus}$ is sparse. Studies of CH_3F ionization and ethane protonation[18b] in "Magic Acid" have, however, been interpreted in terms of $CH_3^{\oplus}$ complexes.

The structure of the ethyl cation in the gas phase and in solution is also of interest. Recent theoretical studies show a modest energetic preference for a hydrogen bridged structure in the gas phase[20a, b], but solvent is expected to interact much more strongly with an open ethyl cation structure, and this is probably favored in solution[20c, d].

Carbocations can be made more stable than $CH_3^{\oplus}$ or $C_2H_5^{\oplus}$ by attaching substituents capable of donating electrons to the positively charged center. Such stabilized carbocations have been the main object of study in the past, but recently there has been increased interest in those species with destabilizing influences. Three classes of these carbocations will be considered; namely those destabilized by structural effects, antiaromatic effects, and by the presence of electron withdrawing substituents[21].

3. Structurally Destabilized Carbocations

Structural distortions that destabilize carbocations arise when the cationic center is prevented from attaining the ideal trigonal geometry. In the solvolyses of the arylcyclopropanes **4** to **5** and the arylnorbornanes **6** to **7**, coplanarity can be attained at the carbocation center, but because the bond angles at the charged atom are constrained to be much smaller than 120° the reactivities are depressed relative to the corresponding cyclohexyl derivative by 2×10^7 for **4** (R = *p*-OCH_3)[22] and 500 for **6** (R = H)[23a, b]. Another example of destabilization of the cations **5** and **7** is the de-



4 **5**

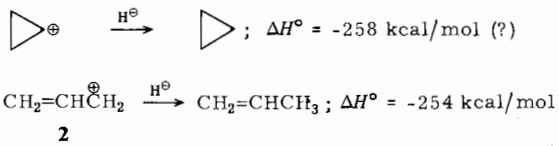
6 **7**

pendence of the reactivities on the aryl substituents; thus the ρ^+ (reaction constant, Brown-Hammett parameter) values for reactions of **4** (X = 3,5-dinitrobenzoate) and **6** (X = Cl) are −7.07[22] and −5.64[23b], respectively, compared to the value of −4.72 for 2-aryl-2-propyl-*p*-nitrobenzoates[22]. The large magnitude of ρ^+ for **4** and **6** was interpreted as arising from a high electron demand originat-

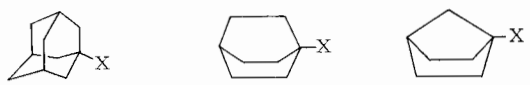
ing from the small bond angles which lead to destabilization of the carbocation.

Comparison of the ρ^+ values of closely related systems is an application of the "tool of electron-demand"[23], and is based on the plausible idea that a less stable carbocation will elicit a greater response from an adjacent substituent. However, the bond angle deformation in **5** or **7** is not relieved by increased electron delocalization from the aryl group. It may be argued that the transition states for these unreactive substrates **4** and **6** are more product-like and hence have greater contributions from the aryl group. Alternatively, the bonds from the carbocation center to the aryl group in **5** and **7** may be somewhat shorter than normal due to the high p character in the endocyclic orbitals, so that more efficient overlap is possible. However, both these explanations are speculative, and this phenomenon is, therefore, worthy of further study.

Calculations using the 6—31G** basis set indicate that the cyclopropyl cation is destabilized by 36 kcal/mol relative to the allyl cation **2**[20e]. However, experimental determination of the proton affinity of cyclopropene gave[24b] a value of 194±3 kcal/mol, which suggests that the $C_3H_5^{\oplus}$ species is only 12 kcal/mol less stable than **2**. If this ion is the cyclopropyl cation, it is not destabilized. On the contrary, it would have a hydride affinity of −258 kcal/mol, which is within the experimental uncertainty of the hydride affinity of **2**. It would appear that the structure and energetics of this system are still not settled and deserve further study.



Bridgehead cations that are geometrically restrained from attaining planarity are also destabilized, as illustrated by the relative solvolysis rates for **8**, **9**, and **10** inter alia[25]. Interestingly, the 1-adamantyl cation derived from **8** is 4



8 (1.0) **9** (10^{-6}) **10** (10^{-11})

kcal/mol more stable in the gas phase than the *tert*-butyl cation[26b]. It was argued[26a] that the destabilization due to strain in the 1-adamantyl cation is not as large as the stabilization provided by the large hydrocarbon framework.

The phenyl cation **11** is structurally destabilized due to the presence of the positive charge in an sp^2 orbital[27,28]. Even although **11** is difficult to form, there is some evidence for the occurrence of this species in reactions of the

11

phenyldiazonium ion inter alia[27,28], including the β-decay method (cf. Section 2)[28a,c].

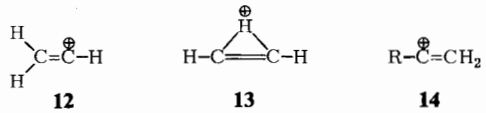
Both thermochemical data[13] and calculations[27c] indicate that the phenyl cation is strongly destabilized. The enthalpy of formation $\Delta H_f^0 = 285$ kcal/mol[13] of $C_6H_5^{\oplus}$ leads to a hydride affinity of −298 kcal/mol, which is of even greater magnitude than that for the conversion of the vinyl cation into ethylene (−287 kcal/mol). It has been suggested[27d] that 270 kcal/mol is a better value for ΔH_f^0 of $C_6H_5^{\oplus}$, but even if this value is adopted the hydride affinity is still comparable to that of $C_2H_3^{\oplus}$.

Vinyl cations are destabilized relative to the corresponding saturated and allylic species as illustrated by the hydride affinities in Table 1[5,29].

Table 1. Hydride ion affinities [kcal/mol] of simple acyclic carbocations [5, 29].

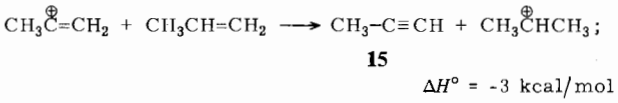
$H_2C{=}\overset{\oplus}{C}H$	−287	$CH_3\overset{\oplus}{C}H_2$	−272
$H_2C{=}\overset{\oplus}{C}CH_3$	−265	$CH_3\overset{\oplus}{C}HCH_3$	−248
$H_2C{=}CH\overset{\oplus}{C}H_2$	−254		

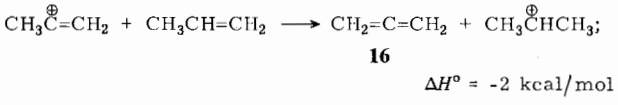
Calculations suggest that in the gas phase the parent vinyl cation $C_2H_3^{\oplus}$ has either the open **12** or bridged **13** structure, separated by a relatively small energy gap[29,30]. The effects of solvation on the preferred geometry are certain to be significant and, hence, it is not possible to predict the preferred structure in solution with confidence. For substituted vinyl cations both calculations and experimental data favor the open ion structure **14**[30–32].



12 **13** **14**

Vinyl cations are particularly readily formed by protonation of alkynes or allenes because of the relatively high ground state energy of the parent hydrocarbons. These effects are illustrated by the small exothermicities of the isodesmic processes for the formation of **15** and **16**[29].





These results are paralleled in solution. Thus in 9.12 M H_2SO_4, propene is protonated only 6.5 times faster than propyne **15** and 37 times faster than allene **16**[31]. A more systematic comparison of alkyne and alkene protonations shows a linear free energy correlation between them (Fig. 1) with a slope $\lg k_{H^+}(\text{alkyne})/\lg k_{H^+}(\text{alkene}) = 1.25$[32]. This correlation is consistent with an open ion structure for the intermediates formed from alkyne protonations, and the slope gives a quantitative measure of the greater effect of substituents in vinyl cations compared to alkyl cations.

Generation of the parent vinyl cation $C_2H_3^{\oplus}$ in solution is an interesting challenge that was first studied by *Ber-*

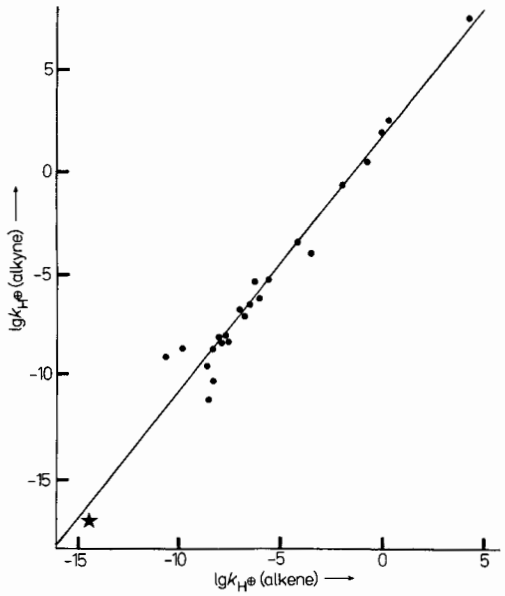


Fig. 1. Linear free energy relationship for protonation of alkenes and alkynes (the star indicates the point for $CH_2=CH_2$ and $CH\equiv CH$).

thelot as long ago as 1862[33]. His studies and those of others over the following 20 years established that in H_2SO_4 acetylene is converted into acetaldehyde, which then reacts further to give crotonaldehyde **17**. More recently, *Olah et al.*[34] showed that the reaction of acetylene with FSO_3H at low temperatures gives the vinyl fluorosulfate **18** which, however, decomposed above $-15\,^\circ C$.

$$HC\equiv CH \xrightarrow{H_2SO_4} CH_3CH=O \longrightarrow CH_3CH=CHCH=O \quad \mathbf{17}$$

$$HC\equiv CH \xrightarrow{FSO_3H} H_2C=CHO_3SF \quad \mathbf{18}$$

We have carried out quantitative studies of the reactions leading to **17** in an attempt to determine whether $C_2H_3^\oplus$ is involved. The ^{1}H-NMR spectrum of $HC\equiv CH$ was recorded at $25\,^\circ C$ in 90—95% H_2SO_4 and observed to display the distinctive signals of acetaldehyde, which is then converted into crotonaldehyde **17**[35]. The formation of crotonaldehyde from acetylene or acetaldehyde can also be monitored by UV spectroscopy under the same conditions. From these results, a relative rate ratio $k(CH_2=CH_2)/k(CH\equiv CH)\approx 200$ for the reaction in strong acid can be estimated. The linear free energy relationship between alkyne and alkene protonations (Fig. 1) predicts a very similar value to this ratio at an acidity $H_0=0$ based on the known reactivity of ethylene[19]. Because an accurate measurement of the acidity dependence of the acetylene reaction is not available, the agreement of the predicted and observed reactivities is only qualitative, but the behavior is certainly that expected from protonation of acetylene to give $C_2H_3^\oplus$.

4. Antiaromatic Carbocations

Carbocations destabilized by antiaromatic effects form a small but important class[36]. Destabilization of the cyclopentadienyl cation **19** in this way is illustrated by its hydride ion affinity of -258 kcal/mol, compared to the value of -225 kcal/mol for **20**[13]. Similarly, the $pK_{R^\oplus}$ of **19** has been reported[36b] to be -40, compared to a value of ca. -20 for the allyl cation. Attempts have also been made to generate **19** by reaction of cyclopentadienyl iodide and

19

20

$Ag^\oplus$, and these experiments showed a kinetic barrier of at least 10^5 relative to the corresponding reaction of cyclopentyl iodide[36d].

5. Electronic Substituent Effects on Carbocations

The most direct measure of the effect of substituents R on the stabilities of ions $RCH_2^\oplus$ is available from gas-phase studies (Table 2)[37] and from calculations (Table 3)[6a]. The data show net stabilization of the carbocation by all substituents studied, except the cyano group. There is good qualitative agreement between the two methods for particular substituents for all cases except fluorine, which is calculated to have only a minor stabilizing effect; in contrast, the gas phase results suggest a stronger influence, almost as great as that of the methyl group.

Table 2. Experimentally measured stabilization energies E_S [kcal/mol] of substituents R in cations $RCH_2^\oplus$ [37a]; values in parenthesis, see [37b].

R	CN	H	F	Cl	CH_3	SCN	Br	I	C_6H_5	OH
E_S	−10 (8)	0 (0)	26	32	35 (42)	42	51	53	55	60 (61)

R	SH	OCH_3	SCH_3	PMe_2	NH_2	NHMe	NMe_2
E_S	64	69 (78)	74	79	95 (95)	99 (108)	106 (110)

Table 3. Calculated stabilization energies E_S [kcal/mol] of substituents R in cations $RCH_2^\oplus$ [6a].

R	H	Li	BeH	BH_2	CH_3	NH_2	OH	F	Ne
E_S	0	79.6	20.4	26.6	29.9	93.3	47.8	2.1	?

More recently there have been a large number of calculations on the effects of particular substituents on cations RCH_2^+[38–41], but perhaps the most comprehensive of these is from *Reynolds, Taft,* and *Topsom* et al.[41]. These authors studied the ability of substituents to donate π electron density to the carbocation centers in $RCH_2^\oplus$ and $RC_6H_4CH_2^\oplus$, as well as in the neutral benzene RC_6H_5, as expressed by the parameter $\Sigma q\pi$ (Table 4). The results indicate that the

Table 4. π-Electron transfer parameters for substituents R in cations $RCH_2^\oplus$ and $RC_6H_4CH_2^\oplus$ [41].

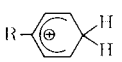
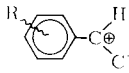
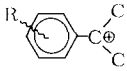
R	NH_2	OH	F	$CH=CH_2$	CH_3
$RCH_2^\oplus$	−566	−486	−353	−427	−113
$RC_6H_4CH_2^\oplus$	−284	−202	−134	−148	− 29
RC_6H_5	−115	− 90	− 70	0	− 8

R	CF_3	CN	CHO	NO_2	H
$RCH_2^\oplus$	− 29	−262	−155	− 76	0
$RC_6H_4CH_2^\oplus$	− 4	− 33	− 20	− 10	0
RC_6H_5	10	21	27	19	0

substituents studied are π electron donors in the cations, with a relatively larger electron donating effect in the $RCH_2^{\oplus}$ system, where electron demand is higher. All the groups that are π acceptors in RC_6H_5 (R = CF_3, CN, CHO, NO_2) are π donors in the cations.

A variety of other aryl systems have been used to study substituent effects, as summarized in Table 5[42–47]. Here, the σ^+ parameters of the substituent R derived[48,49] from the rates of ionization of 2-aryl-2-propyl chlorides ($RC_6H_4CMe_2Cl$) in 90% acetone have been used successfully to correlate the data with the dependence on the substituent parameters measured by the ρ^+ parameter. Comparison of the values of ρ^+ in Table 5 indicates a greater

Table 5. Correlations of substituent effekts in aryl cations by σ^+ parameters.

Cation	Source	ρ^+	Ref.
	gas-phase benzene protonation	−17 [a]	[42]
	calculated	−17	[43]
	gas-phase styrene protonation	−10.7	[44]
	in solution	− 3.6	[45]
	gas-phase α-methylstyrene protonation	− 9.2	[46]
	in solution	− 2.9	[47]
$R\overset{\oplus}{C}HCH_3$	alkene protonation	−10.5	[19b]

[a] Derived from data in ref. [42] and [43].

magnitude of the ρ^+ values in less stabilized systems (*e.g.*, gas versus solution phase; benzene versus styrene protonations; and styrenes versus α-methylstyrenes).

Because the σ^+ parameters have proven so successful in correlating electrophilic reactivity, electronically destabilizing substituents will be defined as those groups with positive σ^+ values. The effects of these substituents in aromatic systems have been thoroughly elucidated, but it is of great interest to examine their effects at the α-position of aliphatic systems such as **21**.

21

For purposes of classification, groups such as CH_2F and CF_3, for which σ^+ parameters from solvolyses of cumyl chlorides are available, are considered as separate substituents, although they could be regarded as β-fluoro- and β-trifluoro-substituents, respectively. A selection of σ^+ parameters is given in Table 6, and recent data are summarized in the following subsections. For some of the substituents, σ_p values are listed because σ^+ values have not been measured. The α-fluoro group, which has a negative σ_p^+ value, is included for purposes of comparison.

Table 6. σ_p^+ Parameters of electron withdrawing substituents [53, 54].

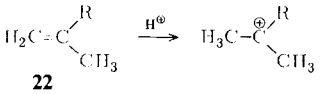
F	−0.07	CN	0.66	CO_2H	0.42
Cl	0.11	NO_2	0.79	CO_2Me	0.49
Br	0.15	$NMe_3^{\oplus}Cl^{\ominus}$	0.41	COMe	0.47
I	0.13	$SiMe_3$	0.02	PO_3Et_2	0.50 [b]
CF_3	0.61	C_6F_5	0.26	$CH_2NMe_3^{\oplus}$	0.50
CH_2F	0.11 [c]	C≡CH	0.18	CH_2OH	0.01
CH_2Cl	−0.01	SO_3R	0.90 [a]		

[a] σ_p-value. [b] cf. [95]. [c] σ_m^+, cf. [50].

5.1. Halogen Substituents

It is well known from studies of electrophilic aromatic substitution that halogen substituents exhibit two opposing electronic effects on carbocation stability; an inductive electron withdrawal and a π electron donation by resonance. Interestingly, both of these effects decrease along the series F > Cl > Br > I; the inductive withdrawal decreases as the halogen becomes less electronegative, and the conjugative effect diminishes as the CX bond becomes longer and hence the overlap between the 2p orbital on the carbon atom and the p orbital on the different halogen atoms becomes successively smaller. The sum of these effects, as measured by the σ_p^+ values, gives a reasonable prediction of the reactivities in the protonation of the 2-halopropenes **22** in CF_3CO_2H[51] or H_2SO_4[52].

Table 7. Relative rates for protonation of halo-substituted alkenes **22**.

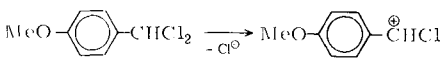


22

R	σ_p^+	CF_3CO_2H [51]	H_2SO_4 [52]
H	0.0	1.0	1.0
F	−0.07	71	54
Cl	0.11	0.35	—
Br	0.15	0.082	0.28

These results contrast with the experimental gas-phase effects of these substituents in $RCH_2^{\oplus}$ ions (Table 2)[37]. In this case, the order of stabilization is I > Br > Cl > F, indicating that strong polarizability effects operate; the stabilizing ability in situations of high demand is therefore determined by the size of the atom. In solution, the electron demand is much less and polarizability effects are not dominant.

Comparison of the results of solvolytic studies of *p*-methoxybenzylidene chloride[53a] with the rates for *p*-$MeOC_6H_4CH_2Cl$[53b] affords a $k(H)/k(Cl)$ substituent effect of 0.1. The greater reactivity of the substrate forming the α-chloro cation is contrary to that expected from the σ_p^+ constant of this group or by analogy with the protonations of **22**.



Similar results were found for $PhCHR_2$ (R = Cl, Br) and for $PhCR_3$[53c]. The rather high reactivity of these latter systems may indicate that ground state strain is significant.

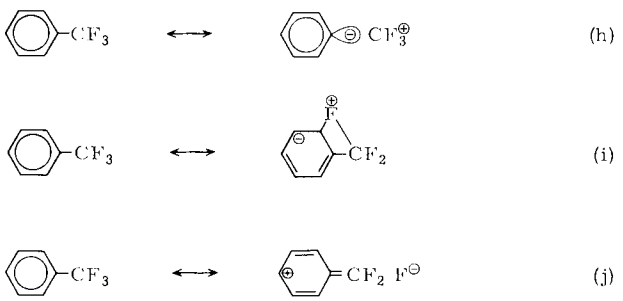
5.2. Halomethyl Groups

The *m*-CH_2F substituent is significantly electron withdrawing as measured by its σ^+ constant[50], whereas the *p*-CH_2Cl substituent is essentially electroneutral[48]. These

groups have not been extensively examined as α-substituents, but the fact that 2-(chloromethyl)propene and propene have approximately the same reactivity in protonations[54] provides powerful confirmation of the applicability of the σ_p^+ parameters derived from aromatic reactivities to aliphatic systems.

The CF_3 group is a strong electron withdrawing substituent as measured by σ_p^+ and has the added virtues of low steric requirements (as measured by van der Waals radii), relative chemical inertness, and wide availability.

According to theoretical studies, the donation of electrons from CF_3 by resonance is predicted to be less than that for other substituents with positive σ^+ values (Table 4)[39,41]. However, there have been two novel proposals for electron donating mechanisms by the CF_3 group: first, to account for the apparent high electron density at the *ipso*-carbon in trifluoromethylbenzene, revealed by photoelectron spectroscopy (cf. (h))[55]; and second the apparent lower electron density at the *para*-relative to the *meta*-positions, which results from the interaction of the n-electrons



(h) (i) (j)

of the F atoms with benzene (cf. (i))[56]—an alternative to the usual hyperconjugative formulation (cf. (j))[57].

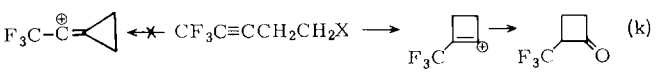
The marked effect of CF_3 on carbocation stability is shown by thermochemical data[58,59], which demonstrate the great destabilizing effect of CF_3 relative to CH_3 and even the H atom.

$$CH_4 + CF_3\overset{\oplus}{C}H_2 \longrightarrow \overset{\oplus}{C}H_3 + CF_3CH_3$$
$$\Delta H_f^{298} = -13 \text{ kcal/mol}$$

$$CH_3CH_3 + CF_3\overset{\oplus}{C}H_2 \longrightarrow CH_3\overset{\oplus}{C}H_2 + CF_3CH_3$$
$$\Delta H_f^{298} = -56 \text{ kcal/mol}$$

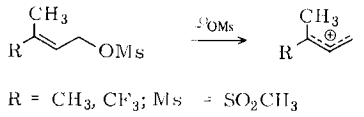
The influence of CF_3 groups on solvolytic reactivity has been studied for more than 20 years, and there is evidence that this substituent is destabilizing in both S_N2[60] and S_N1 reactions[61]. Thus CF_3CH_2I was found to be less reactive than CH_3CH_2I towards attack by C_6H_5SNa by a factor of 1.8×10^4[60a], and $CF_3CH(OBs)CH{=}CH_2$ (Bs = *p*-bromobenzenesulfonyl, "brosyl") was recovered unreacted after 35 d at 50 °C in 70% acetone[61].

The destabilizing influence of the CF_3 substituent also causes the extraordinary long lifetime of the $CF_3CH_2N_2^{\oplus}$ ion in solution[62]. In the reaction of the homopropargyl system in equation (k)[63], only the cyclobutanone derivative was formed, with no trace of cyclopropyl products.



(k)

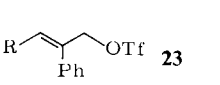
A quantitative measure of the destabilizing influence was provided by the reaction shown in equation (l) where the ratio $k(CH_3)/k(CF_3)$ was found to be 5.4×10^5[64].



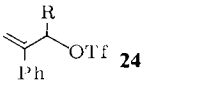
(l)

R = CH_3, CF_3; Ms = SO_2CH_3

Other large rate retarding ratios for CF_3 groups in allylic systems were found by *Harrington* in studies of the systems **23** and **24**[65].



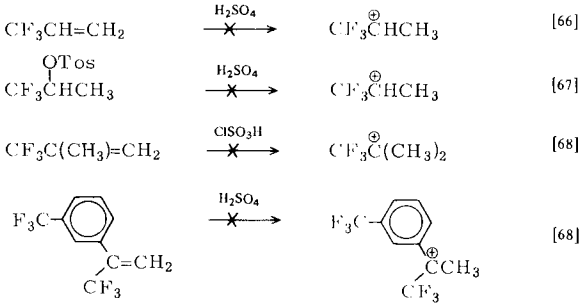
23 $k(H)/k(CF_3) = 3 \cdot 10^3$



24 $k(H)/k(CF_3) = 5 \cdot 10^4$

R = H, CF_3; Tf = SO_2CF_3

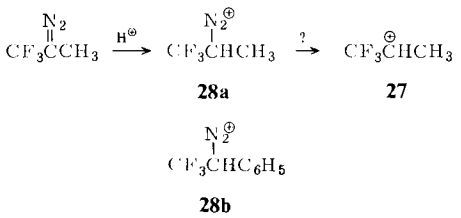
Some seemingly promising methods for forming carbocations presumably failed because of excessive charge destabilization in the ionic intermediates[66–68].



Similarly attempts to generate the ions **25**—**27** for direct detection by NMR spectroscopy were unsuccessful, and only the protonated alcohols were observed[69].

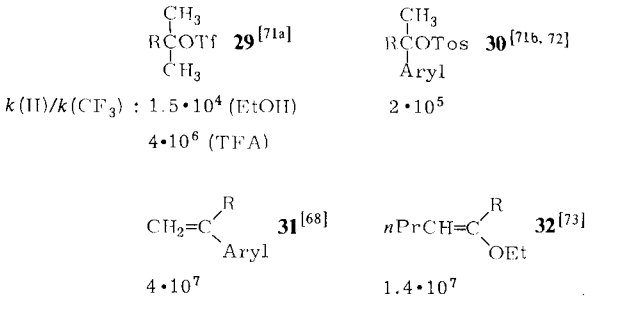
$C_6H_5\overset{\oplus}{C}(CF_3)_2$ **25** $CH_3\overset{\oplus}{C}(CF_3)_2$ **26** $CF_3\overset{\oplus}{C}HCH_3$ **27**

Evidence was obtained[70a] for protonation of 1,1,1-trifluoro-2-diazopropane to give the diazonium ion **28a**, a potential precursor for **27**, but the mode of decomposition of **28a** probably involves solvent displacement. The phenyl derivative **28b** has also been investigated[70b].

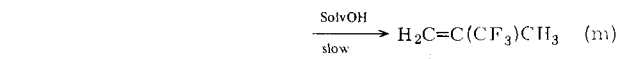


Kinetic studies of CF_3 systems have yielded the $k(H)/k(CF_3)$ rate ratio for solvolysis of the allyl system **24**, as well as those noted for the solvolyses of **29** and **30**, and protonation of **31** and **32**.

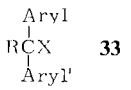
Solvolysis of **29** is markedly dependent on the solvent. In this case ionization may not be the rate determining step, but rather formation of an ion pair which undergoes solvent-assisted elimination (cf. (m)). Evidence for the occur-



rence of this process includes the lack of correlation between the observed rates and the solvent ionizing power, isotope effects $k(CH_3)/k(CD_3)$, and salt effects in 80% EtOH[71a,b].

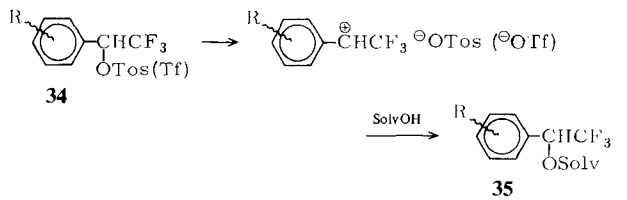


The reactions of **30**, **31**, and **32** all involve rate limiting carbocation formation. The solvolysis of **33** has been studied by *Sneen et al.*[74] and found to form carbocations with a $k(H)/k(CF_3)$ ratio of 3×10^6.



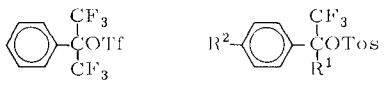
33

Efforts to generate secondary carbocations with α-CF_3 substituents by treating alkenes or alcohols with strong acids have been unsuccessful[66,69]. However, reaction of the sulfonates **34** in a variety of solvents evidently involves carbocation intermediates, as indicated by the dependence of the rates on solvent ionizing power ($m_{OTos} = 0.7$ to 1.0), substituents R ($\sigma^+ = -7$ to -12), secondary deuterium isotope effects [$k(H)/k(D) = 1.20-1.35$], and the essentially complete racemization of optically active **34** (OTos, R=H) in the highly ionizing solvents CF_3CO_2H and $(CF_3)_2CHOH$[75]. However, in the more nucleophilic solvent CH_3CO_2H, 40% inversion occurs in the formation of **35**, suggesting that **34** reacts *via* an ion pair which is preferentially attacked by solvent from the back side. The observed ratios of the rate constants determined by polarimetry and spectrophotometry [9 (CF_3CO_2H) and 1.1 (CH_3CO_2H)] are consistent with this interpretation.



Astrologes and *Martin*[76] established that solvolysis of the trifluoromethanesulfonate ("triflate") **36** bearing two CF_3 substituents involves a carbocation intermediate; however, reference data for related substrates were not available and hence no estimate of the destabilization caused by these groups was possible. We have made further studies of **36** as well as of the related tosylates **37**[77].

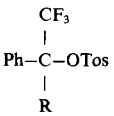
The reactions of **37** ($R = CF_3$) evidently involve carbocation intermediates, such as **25**, as indicated by the strong effect of *para*-substituents on the reactivity ($\rho^+ = -10.7$) and by the dependence of the rate of solvolysis of **37a** on solvent ionizing power ($m = 0.76$), but surprisingly the rate ratio k(**37b**)/k(**37a**) is only *ca.* 3 in several solvents, and the ratio k(**37f**)/k(**37d**), only 1.1. These results were completely unexpected: H/CF_3 rate ratios usually[71-75] lie in the range 10^4 to 10^7, and H/CN rate ratios are 10^2 to 10^7 (cf. Section 5.4), whereas those compounds with two destabilizing groups have markedly smaller ratios.



	R^1	R^2
a	CF_3	OMe
b	H	OMe
c	CF_3	H
d	CN	H
e	CH_3	H
f	H	H

Ground-state steric crowding possibly contributes to the reactivities in these highly substituted derivatives[78,79], but whereas the X-ray crystal structures of **37c—f** reveal[77] significant structural distortions, as evidenced by the bond angles around the central carbon shown in Table 8, the

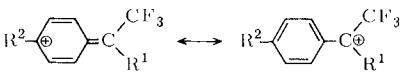
Table 8. Bond angles [°] in α,α-disubstituted benzyltosylates



R	Ph–C–OTos	Ph–C–CF_3	Ph–C–R
CH_3	110	110	114
CF_3	115	109	115
CN	114	111	112
H	110	113	—
R	**CF_3–C–R**	**CF_3–C–OTos**	**R–C–OTos**
CH_3	109	100	113
CF_3	107	102	108
CN	107	102	110
H	—	103	—

structures of all four substrates are rather similar, and no additional strain that would enhance the reactivity of **37c** or **37d** relative to **37f** is apparent. The relationship between structural distortion and the actual energetics of these derivatives is also unknown.

A plausible explanation for the high reactivity of **37a** and **37c** is that for these substrates, as well as for **37f**, the positive charge in the solvolysis transition state largely delocalizes into the aryl ring, as depicted in **38**, and that the rate varies little with the nature of the α-substituent ($R^1 = H$, CF_3). When $R^1 = CH_3$ (**37e**) resonance structure **39** makes a significant contribution and the reactivity is much higher.



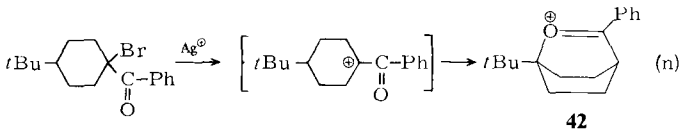
A similar explanation could hold for the high reactivity of **37d** (R^1 = CN); here, charge delocalization to the CN group could also be significant.

5.3. α-Carbonyl Substituents

α-Carbonyl groups have long been used in preparative methodology, and more recently have been the subject of mechanistic studies. An interesting early example[80] was the hydride migration **40** → **41**, which shows a 2.8fold preference for hydrogen over deuterium migration. The acid-catalyzed decomposition of α-diazoketones is the most commonly used reaction to prepare such species[81,82].

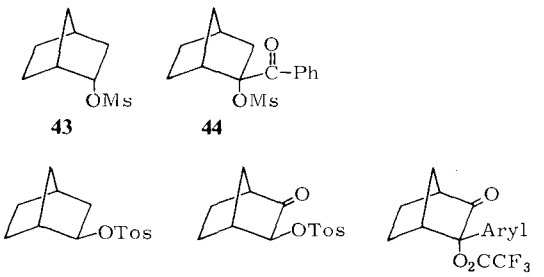
40 **41**

The ionization of α-haloketones has also been the subject of recent studies[83,84], including the example shown in reaction (n)[83], which presumably involves an α-keto carbocation intermediate that rearranges *via* hydride shifts to **42**.



42 (n)

Theoretical studies[39a] suggest that $\overset{\oplus}{C}H_2CHO$ is destabilized less (relative to $\overset{\oplus}{C}H_3$) than $\overset{\oplus}{C}H_2CF_3$ (9.9 and 37.3 kcal/mol, respectively), and kinetic studies[85] also indicate that α-carbonyl groups do not affect solvolysis rates as much as CF_3 groups. Thus, the ratio of rate constants k(**43**)/k(**44**) is *ca.* 8[85c] compared to values of 10^4—10^7 for k(H)/k(CF_3). The ratio k(**45**)/k(**46**) is 6×10^5.



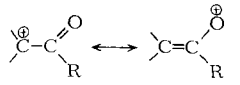
43 **44**

45 **46** **47**

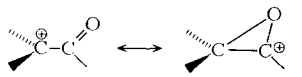
That carbocations occur as intermediates in these solvolyses is supported by ρ^+ values of −7.1 for the acetolysis of **47**[85a] and −5.69 for ethanolysis of the analogous methanesulfonate (mesylate)[85b], and also by the dependence of the rates on the solvent ionizing power (m = 0.67 to 0.91).

Several explanations for the relatively small destabilization by the α-carbonyl group were considered, but the most favored was that delocalization of positive charge to the carbonyl group occurred (**48**)[85c].

This interpretation is supported by theoretical studies[39]. The structure **48** implies that the carbonyl group and the carbocation center are coplanar; calculations on $C_2H_3O^{\oplus}$ suggest that in the gas phase the oxiranyl structure is preferred[85d,e].

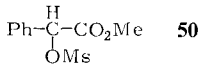


48



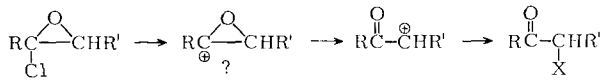
49

Arguments against **49** include the facts that optically active **50** undergoes trifluoroacetolysis with racemization and that acetolysis occurs with 11% net inversion[85c]; in contrast, structure **49** would favor retention. The ions from **46** or **47** are also geometrically precluded by the geometry of **49**. The study of a suitable substrate which cannot undergo the resonance interaction shown in **48** would be of interest in this respect.

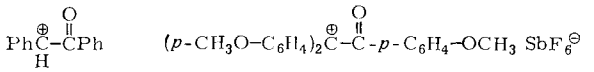


50

The ionization of α-chloroepoxides provides a potentially alternative route to carbocations of the oxiranyl and α-keto type[86]. It was suggested[86b] that in some cases these reactions involve direct ionization to the α-keto structures without the intervention of the oxiranyl ions, but the generality of this mechanism has not been established.



Several long-lived α-carbonyl carbocations have been observed directly by NMR spectroscopy[87], including the secondary species **51**[87c]; **52** has been isolated as a pure crystalline solid[87a].



51 **52**

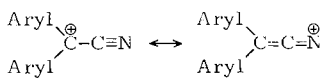
The fact that the values of m for the α-carbonyl derivatives and for the α-CF_3 substituted compounds **34** are less than 1.0 is of interest since a strong dependence of reaction rate on solvent ionizing power might have been expected for these destabilized species. A plausible explanation of this behavior for **34** is that in the transition state significant charge delocalization onto aryl groups occurs and that the influence of the solvent is less. Delocalization of positive charge onto carbonyl as in **48** might similarly result in a rather small value of m for α-carbonyl systems.

The low m-values for the solvolyses of these systems with destabilizing substituents are important for the proposal that low m values observed in certain other systems indicate intervention of the "S_N2-intermediate" mechanism[8] involving back side solvent participation. There is

strong evidence that this mechanism is not involved with these destabilized compounds, including the observation that the optically active **34**[75] and **50**[85c] undergo solvolysis with considerable racemization. Thus, low *m* values *per se* are not diagnostic of mechanisms involving direct solvent participation.

5.4. The α-Cyano Substituent

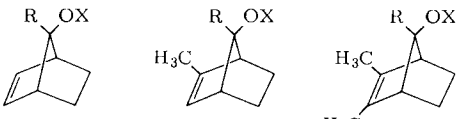
The effect of the α-cyano group has been the subject of several theoretical studies[38-41]. There is general agreement that resonance electron donation by this group will be significant in situations of high electron demand, as illustrated in **53**. Calculations indicate[39,41] that the cyano is a better π donor than the carbonyl group, although the net destabilization by the cyano group is predicted[39a] to be greater because of a greater negative induction effect. The ^{15}N chemical shifts of α-cyano carbocations are consistent with participation of resonance structure **53**, in that substantial positive charge density on nitrogen is detected[88]. Unfortunately, only diaryl derivatives have proven amenable to such NMR studies, and hence the expected higher charge densities on nitrogen in more destabilized systems cannot be established.



53

Solvolysis studies[89-91], as well as the rate of protonation of one cyanoalkene[73] are in accord with variable π electron donation from the cyano group to an adjacent carbocation center, as illustrated by the $k(H)/k(CN)$ ratios for **54—67** (Table 9). A qualitative trend was clear in that the more stabilized systems **59**, **60**, and **65** showed significantly larger $k(H)/k(CN)$ ratios that were comparable to the previously mentioned $k(H)/k(CF_3)$ ratios. This trend was placed[73] on a quantitative basis since a reasonable linear free energy correlation exists between ρ^+ and γ^+ of the cyano group[73]; here the ρ^+ value is derived from the corresponding aryl series and the γ^+ value is defined by $\lg k(CN)/k(Ph)$ versus ρ[92-94]. However, this relation fails badly for **63**, which was reported[91] after the correlation had been published. One reason for this deviation could be a significant steric effect on either the value of ρ^+ or γ^+ for **63**; such an effect would not be accounted for in this treatment.

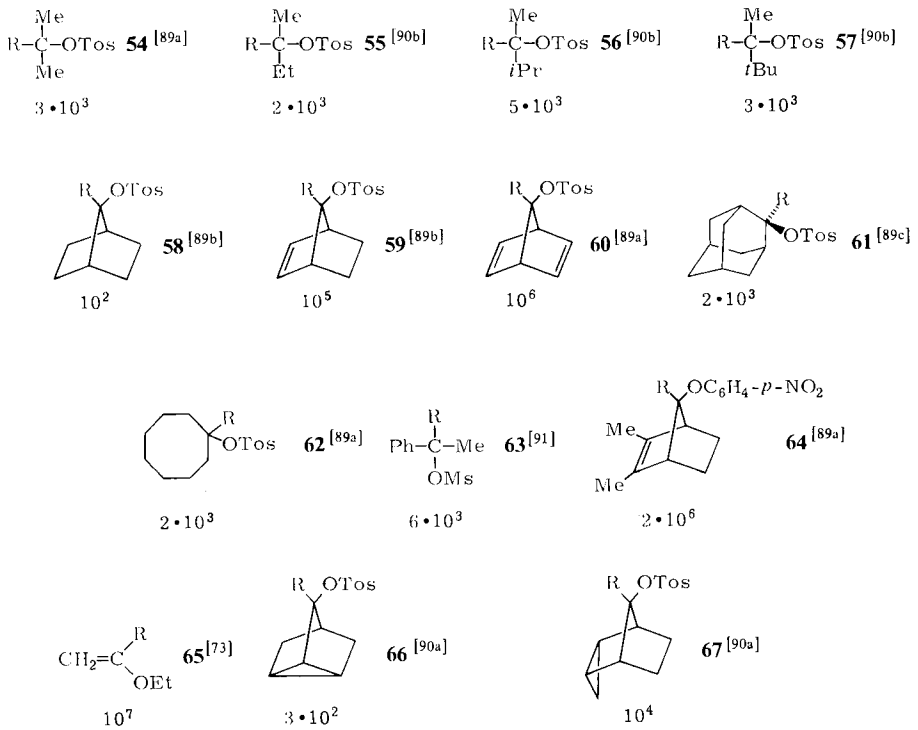
The ρ^+ value for **63** (−6.7) is quite comparable to those found for the α-CF_3 system **30** and the α-carbonyl system **47**. However, the $k(H)/k(CN)$ ratios are significantly larger than the corresponding ratios for the α-carbonyl systems, and in several cases are comparable to the $k(H)/k(CF_3)$ values.



59 **68** **69**

The reactivity of the substrates **59**, **68**, and **69** revealed relative rates of 1:10:150 (R=H) and 1:90:4000 (R=CN). The greater dependence of the system destabil-

Table 9. Ratio of rate constants $k(H)/k(CN)$ for solvolysis of compounds **54-67** (R=H, CN).

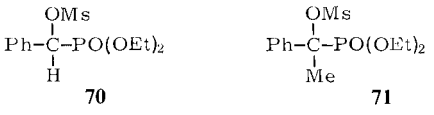


54[89a]	**55**[90b]	**56**[90b]	**57**[90b]
$3 \cdot 10^3$	$2 \cdot 10^3$	$5 \cdot 10^3$	$3 \cdot 10^3$
58[89b]	**59**[89b]	**60**[89a]	**61**[89c]
10^2	10^5	10^6	$2 \cdot 10^3$
62[89a]	**63**[91]	**64**[89a]	
$2 \cdot 10^3$	$6 \cdot 10^3$	$2 \cdot 10^6$	
65[73]	**66**[90a]	**67**[90a]	
10^7	$3 \cdot 10^2$	10^4	

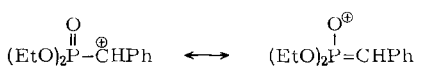
ized by the cyano group on the electron donating ability of the double bond represents another example of the response of such carbocation systems to electron demand.

5.5. The α-Diethoxyphosphoryl Substituent

The σ_p^+ constant of the α-diethoxyphosphoryl group (Table 6) indicates that it is a stronger electron withdrawer than α-carbonyl substituents. Recent experimental studies[95] demonstrate that **70** and **71** react via carbocationic intermediates with $k(H)/k(PO_3Et_2)$ ratios of 10^3 and 2×10^2, respectively. The authors concluded that these differences in rates indicate some electron donation from the phosphoryl group to the carbocation center involving a d orbital on phosphorus (cf. resonance structure **72**). Unfortunately no theoretical studies of this interaction have yet appeared, and hence the interpretation is still tentative.

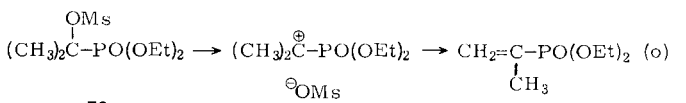


70 **71**



72

Solvolysis of **73** was proposed to occur with the elimination step being partially rate-limiting (cf. (o)). *Creary* et

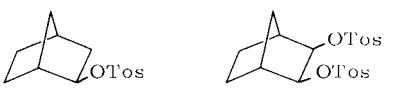


73

al.[95] pointed out this was a cationic analogue to the well known E1cb mechanism and accordingly designated this two-step elimination via a carbocation intermediate as the $E2_{R^+}$ mechanism.

5.6. The Tosyloxymethyl Substituent

No σ_p^+ value is available for the tosyloxymethyl group, but the value is expected to exceed that of the hydroxymethyl group (−0.01). There have been extensive solvolytic studies of 1,2-ditosylates in which one tosyloxy substituent influences the tosylate ionization reactivity[96]. One example is the rate ratio $k(\mathbf{45})/k(\mathbf{74})\approx4\times10^6$.

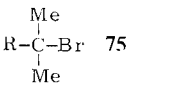


45 **74**

This is comparable to the ratio $k(\mathbf{45})/k(\mathbf{44})$ (cf. Section 5.3), showing that the tosyloxymethyl group has a similar destabilizing effect as the α-carbonyl group.

5.7. α-Silyl Substituents

The σ_p^+ value of 0.02 for the Me_3Si group suggests that this substituent will mildly deactivate a carbocation relative to hydrogen. Relative rate data for solvolysis of **75** in 60% EtOH are shown[97].



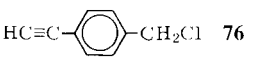
75

R	H	Me_3C	Me_3Si
k_{rel}	1	$4\cdot10^4$	1.0

These data demonstrate that Me_3Si is strongly destabilizing relative to Me_3C, but, since the rate of solvolysis of 2-propyl bromide under these conditions is probably increased by nucleophilic solvent participation, it cannot be conclusively stated that Me_3Si favors carbocation formation relative to H. Recent results on the effects of Me_3Si on S_N2 reactivity have been reported[98], but more data are needed on the behavior of this group in S_N1 type reactions. Calculations indicate that $CH_3\overset{\oplus}{C}H_2$ is 13.2 kcal/mol more stable than $SiH_3\overset{\oplus}{C}H_2$, which is in turn 16.1 kcal/mol more stable than $CH_3^{\oplus}$[98].

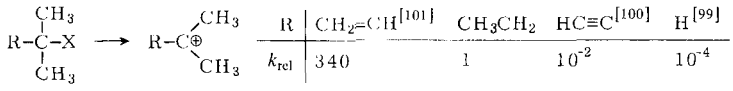
5.8. The Ethynyl Substituent

A σ_p^+ value of 0.18 has been derived for the C≡CH group based on the solvolysis of the *p*-substituted benzyl chloride **76** in 50% ethanol[99]. However, the ρ^+ value for this solvolysis is only −1.7[99], and it appears highly likely that nucleophilic solvent participation is important in this reaction; the derived σ_p^+ value may, therefore, not be reliable.



76

Relative solvolysis rates for **77**[100,101] show that the order of cation stabilizing ability is $CH_2{=}CH > CH_3CH_2 > HC{\equiv}C > H$.



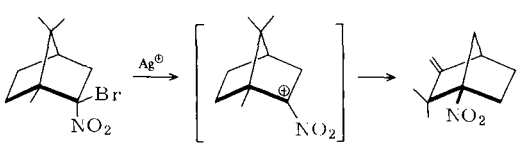
R	$CH_2{=}CH$[101]	CH_3CH_2	$HC{\equiv}C$[100]	H[99]
k_{rel}	340	1	10^{-2}	10^{-4}

77

Taken together, the results for **76** and **77** indicate that the ethynyl group is, at best, a modestly stabilizing group that may be destabilizing in some circumstances. The stabilizing effect of the ethynyl group relative to a hydrogen atom probably represents a minimum value because the reaction rate of the unsubstituted compound is increased by solvent participation.

5.9. Other Substituents

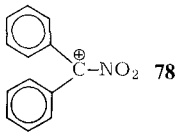
As yet no quantitative data is available for the effects of other destabilizing substituents such as NO_2, $NR_3^{\oplus}$, or SO_3H on the kinetics of formation of carbocation intermediates in aliphatic systems. The reaction of an α-bromonitrobornane [equation (p)] has been observed[102a] and attri-



(p)

buted to intervention of the corresponding α-nitro carbocation.

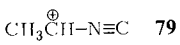
The long-lived species **78** has also been detected in solution and found to have a significant electron deficiency on the central carbon as indicated by its ^{13}C chemical shift[102b].



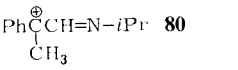
78

Theoretical studies of the $NH_3^{\oplus}$ substituent suggest that some π electron donation from this group is possible[39a,41], and some evidence for this effect has been found in the nitration of benzene substituted with this group[103a].

Two other potentially destabilizing substituents whose effects on carbocations have attracted interest are the isocyano group[103b], which was calculated to be stabilizing relative to hydrogen in **79**, and the α-imidoyl group[103c]; carbocations containing the latter were evidently generated by ionization of the corresponding chlorides to give intermediates such as **80**.



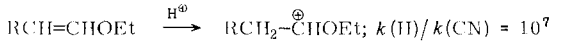
79



80

5.10. β-, γ-, and δ-Substituents

There is abundant evidence that carbocations are also destabilized by electron withdrawing substituents located in the β-, γ-, or δ-positions, or even further removed. Solvolyses of this type have been particularly well examined in the norbornyl system[104], but as this evidence has been recently reviewed[104] it will not be discussed here. It is, however, worth noting that similar effects are observed in alkene protonations[105-107].



$RCH{=}CHOEt \xrightarrow{H^{\oplus}} RCH_2{-}\overset{\oplus}{C}HOEt;\ k(H)/k(CN) = 10^7$

$; k(H)/k(CN) = 10^5$

5.11. Long-Lived Destabilized Ions

Long-lived carbocations substituted with the destabilizing groups CF_3[102b], CN[88], NO_2[102b], CO_2Me[87d], and COPh[87a,d] have been detected by ^{13}C-NMR spectroscopy, and the chemical shifts of their cationic carbon atoms are shown in Table 10, together with some other values[87d] for reference. There is clearly no simple relationship between the destabilizing effect of a substituent and the chemical shift. Thus, based on reactivity studies (cf. Section 5.2) the CF_3 group is more destabilizing than an H atom or the COPh group, although the cationic carbon α to CF_3 is at higher field. However, it is known that even "simple" substituents such as CH_3 affect chemical shifts by more than one mechanism[108a], and there is other evidence for this with a variety of other systems and substituents[108]. There is some indication that chemical shifts are correlated with calculated charges on the cationic carbon[87d], so that a combination of these methods may give a better understanding of these cationic systems.

Table 10. ^{13}C-NMR chemical shifts (δ-values relative to TMS) for the cationic carbon atom in $Ph_2\overset{\oplus}{C}R$.

R	CF_3	CN	NO_2	CO_2CH_3	COPh	H	CH_3
δ	189.6	168.8	189.1	191.2	202.8	199.4	229.3

6. Conclusions and Outlook

Destabilized carbocations have structural features which predestine them to be only transient species. Their study has therefore made valuable contributions to understanding the principles of organic chemistry. In recent years, the study of these species has advanced rapidly through the use of a combination of kinetic studies in solution, theoretical calculations, and structural studies. Several important substituents, most notably NO_2, SO_3R, and $NR_3^{\oplus}$, have been subjected to only minimal quantitative study as destabilizing substituents in aliphatic carbocations and deserve further attention. Many useful applications of destabilized carbocations in syntheses[109] have already been found but many more are to be expected in future. The effort that has been expended in this area has been amply rewarded by the fascinating chemistry that has been revealed, and no less is to be expected for further studies.

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Nodal Nomenclature II—Specific Nomenclature for Parent Hydrides, Free Radicals, Ions, and Substituents**

By Noël Lozac'h and Alan L. Goodson*

Nodal nomenclature is compared with classical organic nomenclature, and the procedure by which an organic compound is given a nodal name is described. Parent hydride—especially hydrocarbon—names are derived from the names of structure graphs and are modified to incorporate descriptions of heteroatoms, unsaturation, free valences, and ionic charges. It is also shown how the substitutive method, though not an integral part of the nodal system, may nevertheless be used as a way to simplify the structure graphs without impairing the logic of the nodal system. For this purpose, it is indicated how to use prefixes or suffixes generally formed according to IUPAC Rules. The rôle of substitution in organic nodal nomenclature is more restricted than in classical nomenclature because many classical substituents are treated as part of the parent hydrides. The concept of "characteristic group" is not used in nodal nomenclature for similar reasons, and the term "principal substituent" is preferred to "principal characteristic group".

1. Preface

The general tendency of classical organic nomenclature, which is the natural outcome of the historical development of organic chemistry, is to consider first the chemical nature of the atoms constituting a molecule and then to indicate how these atoms are connected together. Classical systematic organic names generally correspond to a molecular formula and are sometimes directly derived from this formula (*e.g.*, silane). Nodal nomenclature, on the other hand, can be compared with a technique used for constructing large buildings. It first creates a framework (*i.e.*, a mathematical description of a chemical structure[1]) to which it adds the detail necessary to complete a usable chemical name. Just as new techniques made possible the construction of skyscrapers, so the new concepts of nodal nomenclature facilitate the description of large chemical structures.

The preceding paper[2] of this series, to which we shall refer hereafter as Part I, showed how the framework is created by reducing chemical structures to graphs and then numbering and naming the graphs. This technique of reducing a problem to a graph and then resolving the problem by manipulating the graph is common in graph theory[3,4].

The names of the chemical structures are obtained by supplementing the description of the corresponding graphs, as indicated in Part I, with purely chemical information defining the nature of the atoms and bonds. The objective of this second paper is therefore to describe how parent hydrides—generally organic—as well as their derivatives containing free valences, ionic centers, or substituents can be named by modifying the names of the graphs. For this purpose, it is practical to use, as far as possible, prefixes and suffixes having well known chemical meanings, such as those codified in IUPAC Rules for Nomenclature of Organic Chemistry[5]. To help the reader understand how names of parent hydrides are derived from those of the corresponding graphs, many of the examples in this paper are related to the examples in Part I.

First of all, two important facts should be noted:

1) This paper describes *one* procedure for using nodal nomenclature in organic chemistry, but other procedures such as those involving polynuclear nodes, as in cyclophane nomenclature, can also apply the general method described in Part I, provided that the principles governing the choice of nodes are clearly defined.

2) The Rules concerning substituents, ions, and free radicals show how the main principles underlying IUPAC Rules are applied to parent hydrides named according to the nodal system. In elaborating these Rules, the Authors have drawn great benefit from the work accomplished by the IUPAC Commission on Nomenclature of Organic Chemistry. However, some of these proposals, although consistent with the general methods of IUPAC Rules, represent only the Authors' preference among various possibilities considered by IUPAC.

2. Introduction

It has been argued that the description of the graph, as given in Part I, leads to long strings of numbers and punctuation marks and accordingly is not practical for common use. Some explanations are therefore necessary.

Nodal nomenclature provides a unique and sequential numbering for any graph. The fact that this numbering is unique avoids, in indexes, the scattering of information for compounds having the same carbon skeleton. The fact that it is sequential renders it directly available for construction of a connection table and for substructure retrievals by procedures comparable with those used in the DARC and CAS ONLINE systems. This unique and sequential numbering is intimately connected with the descriptors which were discussed in Part I[2]. The typographical conventions

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[**] Part I ("Nodal Nomenclature—General Principles") see [2].

used for the descriptors were adopted to facilitate understanding of the structure under consideration.

Since we claim that nodal nomenclature is of general use, it is essential for us to show that it works with complicated structures where existing nomenclature rules often do not provide any clear guidance. One should compare only what is comparable, and the "simplicity" of nodal nomenclature should be tested on examples where existing rules provide clear answers. For this reason, we have chosen, for many examples in this paper, compounds that are also used as examples in the IUPAC rules[5]. Thus, nodal nomenclature rules are compared directly with existing IUPAC rules.

There are two questions which must be borne in mind during the further development of nodal nomenclature.

The first is the perennial difference in nomenclature requirements between the primary literature and that of an index.

An essential question for indexing and information retrieval is whether the nomenclature system used leads to a unique and unambiguous name for any given chemical structure. IUPAC Rules often provide various possible names for a substance and, owing to the fundamental inconsistencies of traditional methods, the choice of unique "official names" often requires that the user define his own selection rules. On the other hand, nodal nomenclature can define clearly, for indexing and information storage and retrieval purposes, a unique and unambiguous name for any molecule, provided that the principles governing the choice of nodes and of substituents are clearly defined.

In the primary literature, an author may name a substance to reflect the nature of the work being described. Another author may name the same substance differently because the nature of the work he is describing is different. Therefore, primary literature requires only that names be unambiguous, while indexes require not only unambiguous but, as far as possible, unique names. Some flexibility is built into nodal nomenclature so that while unique names can be derived for indexing purposes, shorter, more convenient names will also be available for use in the literature.

This leads to the second question that must be borne in mind. It is generally recognized that existing nomenclature practices are in need of improvement. When a new nomenclature system is developed and proposed, there is always the potential for conflict between the needs of the chemist and the needs of the information retrieval specialist. It is possible to make minimal (but frequent) changes to existing nomenclature practices and thus retain procedures and names with which the chemist is familiar and with which he therefore feels comfortable. The information retrieval specialist, on the other hand, would prefer a completely systematic nomenclature system that never needs modification and yields unambiguous names as simple as the complexity of structures permits. In developing nodal nomenclature, we are trying to strike a balance between these two extremes and that is why we show how the substitutive method may be used in nodal nomenclature.

Use of the substitutive method is not essential in nodal nomenclature but is advisable for two reasons. The first is that removal of substituents simplifies the graph and, accordingly, its name. The second reason is that chemists will prefer to relate simple substituted structures to the graph of the unsubstituted one; for example, most chemists will prefer to relate a chlorohydrocarbon to the graph of the unsubstituted hydrocarbon. For a similar reason, indexes require that names of related substances be grouped together. For this purpose a compound commonly named as "2-chloro-1-butanol" is frequently given the inverted name "1-butanol, 2-chloro-" in an index. There is no particular problem for applying this procedure to substitutive nodal names.

It is important to remember that the following Rules are modular because of the underlying logic of nodal nomenclature. This means that the various features of a chemical compound are described successively, in a prescribed order, by prefixes and/or suffixes, and that any new feature can influence the numbering of the skeleton only if the preceding features have left a choice.

A parent hydride is named first, and this gives a high priority to unsaturation for the definition of the numbering. The corresponding Rules are particularly detailed as they constitute the basis of any nodal name.

Next comes the description of free valences and ionic centers on skeletal atoms. It should be remarked that any free valence must belong to a skeletal atom and that the use of "onia" replacement prefixes, according to IUPAC **Rule B-6.1**[5], is not recommended because the neutral parent compound should be completely defined before considering ionic centers.

Last comes the naming of substituents, considered in the order of seniority: anionic, cationic, neutral. Nodal nomenclature sets relatively stringent limits to the use of substituents (**Rule N-10.1**) as well as to the rôle of substituents in name selection. For instance, in nodal nomenclature, no substituent plays a rôle as important as the "principal group"[5a] in IUPAC Rules for acyclic compounds. Accordingly, the term "principal substituent" is preferred for a substituent named by a suffix and having priority for low locants only over other substituents.

For sake of consistency, exceptional treatment of various characteristic groups is avoided and substitutive prefixes are used more extensively than in IUPAC nomenclature (*e.g.*, for aldehydes, ketones and nitriles). For the same reason, radicofunctional names are not used at all (*e.g.*, for esters and acyl halides). When appropriate prefixes are not available in current nomenclature, groups of substituents are named with one locant only, such as "(Mercapto, oxo)" for [C](O)SH in *S*-thiocarboxylic acids, "(Amino, oxo)" for [C](O)NH_2 in carboxamides, "(Chloro, oxo)" for [C](O)Cl in acyl chlorides. This procedure has the advantage that the functional group can be identified easily, without departing from the general substitutive method.

3. Glossary

Many terms used in this paper have already been defined in Part I[2a]. Some additional definitions are necessary for specific nodal nomenclature.

Mononuclear Node: (see: Node[2a]) Used principally to distinguish nodes corresponding to single skeletal atoms from polynuclear (contraction) nodes.

Parent Element[6]: An element whose identity is indicated at the end of the name of a saturated parent hydride. Other elements, if present, are denoted by replacement prefixes such as oxa or aza. The parent element is the most, or one of the most, common in the skeleton. When the skeleton contains equal numbers of atoms of more than one element, including carbon, carbon is preferred as the parent element. If carbon is not among the most common elements of the skeleton, then the parent element is the first cited in Table 3. The concept of parent element applies to graphs containing only mononuclear nodes.

Parent Hydride: In organic nodal nomenclature, the element hydride obtained through replacement by hydrogen atoms of all the atoms or groups considered as substituents. According to this definition, while unsaturation endings (*e.g.*, ene, yne) are part of the parent hydride name, suffixes for principal substituents are not, which is different from IUPAC Rules concerning principal characteristic groups. For this reason, in nodal nomenclature, the term "parent hydride" is preferred to "parent compound" in order to avoid confusion with existing IUPAC terminology.

Polynuclear Node: (see: Contraction Node[2a]) Used principally to stress the polyatomic nature of contraction nodes and to distinguish them from mononuclear nodes.

Principal Substituent: A substituent named as a suffix and having priority for low locants over other substituents (see Table 2). The term "principal substituent" is used in nodal nomenclature in order to avoid confusion with the term "principal characteristic group", which has a different use in IUPAC Rules.

Satellite Atom: A univalent atom (usually hydrogen) attached to a skeletal atom and not regarded as part of the structure graph.

Skeleton: The structure resulting when the nodes and lines (or connectivities) of a structure graph are specified. It contains neither satellite atoms nor substituents.

Substituent: An atom or group that replaces a hydrogen atom of a parent hydride. The following may be named as substituents in organic nodal nomenclature (see Tables 1 and 2): a) a heteroatom which may be linked to hydrogen, or b) a group of heteroatoms which may be associated with carbon (as exceptions), which may be linked to hydrogen and which does not need internal numbering for defining its structure. Use of substitution is therefore restricted in nodal nomenclature. The IUPAC concept of characteristic group is not used in nodal nomenclature.

4. General Concepts of Specific Organic Nodal Nomenclature

For naming purposes, a chemical substance can be regarded either as a neutral parent hydride or as being derived from a neutral parent hydride by introduction of free valences, ionic charges, or substituents. Use of nodal nomenclature to name a chemical substance proceeds in four steps:

1) Definition of the Structure Graph;
2) Numbering and Naming of the Structure Graph, according to Part I;
3) Specification of the Nodes and Lines (*i.e.*, naming the neutral Parent Hydride according to **Rules N-11, N-12** and/or **N-13**);
4) Addition of Remaining Information, if any.

4.1. Definition of the Structure Graph

The structure graph is defined by 1) removing the atoms or groups that are to be treated as substituents, 2) removing the satellite atoms (generally hydrogen), 3) ignoring charges, bond values, free valences, and the identity of skeletal atoms, and 4) defining the nodes as either mononuclear (single atoms) or polynuclear (*i.e.*, contraction nodes representing, for example, benzene or pyrrole rings). In this paper we limit ourselves solely to the use of mononuclear nodes.

At this stage, the operation which is most open to discussion is the definition of substituents. As already stated in the Introduction, use of the substitutive method is not essential to nodal nomenclature but may be considered advisable by many users. That is why, in the proposed Rules, two lists of atoms or groups are given which the Authors believe are advantageously treated as substituents in nodal nomenclature. However, it should be stressed that these lists are not limitative and that further development of nodal nomenclature may demonstrate the need to define larger, but limitative, lists of substituents.

It should also be stressed that this graph-based nomenclature precludes the use of radicofunctional names such as those generally used for esters. Binary names of this

kind are reserved for substances, such as salts, comprising a loose association of structurally independent chemical entities.

4.2. Numbering and Naming of the Structure Graph

This step has been described in Part I[2].

4.3. Specification of the Nodes and Lines: Parent Hydrides

Once the structure graph has been numbered and named, the graph name is modified to include information specifying the nodes and lines. For this purpose, the end of the graph name is changed to indicate the nature of the parent element. Other elements, if present, are denoted by replacement prefixes[5b] such as "oxa" and "aza". Unsaturation is indicated by suffixes: either by the traditional terms "ene" and "yne" with their usual meaning of double and triple bond, respectively, or by the new terms "arene" or "axene" denoting unambiguously the presence of the maximum number of noncumulative double bonds. A summary of the Rules indicating how these various features intervene in the choice of the numbering of a substance is given in **Rule N-14.2.** The resulting name is that of the parent hydride, for instance a hydrocarbon.

Only when all the nodes of a graph have been defined and the nature of the lines has been described is hydrogen formally added to satisfy the valence of each skeletal atom. This valence is the "normal valence"[5c] unless otherwise stated[7].

The systematic numbering of structures is a prominent characteristic of nodal nomenclature which endeavors to treat the same problem in the same way, without reference to peculiarities of structure already considered (modularity principle). This uniformity of treatment contrasts with some IUPAC Rules. A particularly important example concerns numbering of heteroatoms in replacement nomenclature. The nodal system retains the method used by IUPAC[5] for acyclic (**Rule C-62.1**) and polycyclic structures (**Rule B-4.2**) but not the method applied to monocycles (**Rule B-4.1**), which is different.

4.4. Addition of Remaining Information

Once the parent hydride name has been formed, the substance name is derived, if necessary, by addition of the remaining information, such as free valences, ionic charges, substituents, stereochemistry, and isotopic modifications. This implies rules for assignment of locants to the diverse features under consideration.

Application of the modularity principle in nodal nomenclature leads unavoidably to rules rather different from those of IUPAC nomenclature. This is particularly significant for principal characteristic groups as defined in the IUPAC Rules. The nodal system treats all unsaturation before considering substituents, even if these are named as suffixes, while IUPAC Rules do not separate these different issues. For instance, according to **Rule C-15.1**[5], indicated hydrogen has priority over principal characteristic groups, which, in turn, have priority over multiple bonds. Apart from this point, the nodal method is rather similar to the one used by IUPAC for polycyclic systems, where, for instance, heteroatoms are considered before principal characteristic groups for assignment of low locants. This is quite different from the IUPAC practice for acyclic systems, where principal characteristic groups have priority over heteroatoms, not only for assignment of low locants (**Rule C-62.1**[5]), but also for determining the principal chain (**Rule C-63.1**[5]).

The rules proposed in this paper show how it is possible to deal with free valences, ionic charges and substituents, but do not consider stereochemistry and isotopic modification, like Sections E and H of the IUPAC Rules[5]. It seems that there is no particular problem in applying these IUPAC Rules to nodal names and one can note only that nodal numbering facilitates their application because each locant occurs only once.

As for specification of free valences, ionic charges, and substituents, two different problems have to be solved: first, the choice of a terminology; second, the definition of the rules governing the numbering of the substance.

For the first problem, the terminology defined in existing IUPAC Rules[5] is available and only minor decisions have to be made. A nonlimiting set of substituent names is given in **Rule N-10**, and terms denoting free valences and ionic charges are recalled in **Rule N-14.3**.

For the second problem, **Rules N-14.3** and **N-14.5** indicate how free valences, ionic charges, and substituents can affect the definitive numbering of a substance.

5. Proposed Rules for Specific Nodal Nomenclature

Rule N-10—Substituents

N-10.1. Substituent groups should not contain an unbranched chain of more than three atoms other than hydrogen and should not need internal numbering. If a hydrogen atom of such a group is substituted with a group containing the parent element, then the resulting group is not regarded as a substituent but as a part of the parent hydride. A nonlimiting list of acceptable substituent atoms and groups cited only as prefixes in nodal nomenclature is given in Table 1.

N-10.2. Substituents are generally named as prefixes, but groups susceptible to losing a proton, and the corresponding anionic atoms or groups, are named as suffixes under the conditions stated in **Rule N-14.1.** If these conditions are not fulfilled, prefixes are used. A nonlimiting list of acceptable hydrogen-containing substituents which may be cited either as prefixes or as suffixes in nodal nomenclature is given in Table 2.

N-10.3. Substitutive prefixes can be derived from the names of mononuclear hydrides (see Table 3) of elements having a nonstandard classical valence bonding[7].

Examples (substituents cited in Table 1):

1. $-ICl_2$ Dichloro-λ^3-iodanyl
2. $-I(OH)_2$ Dihydroxy-λ^3-iodanyl
3. $-SF_5$ Pentafluoro-λ^6-sulfanyl
4. $-SF_2Cl$ Chlorodifluoro-λ^4-sulfanyl
5. $-SCl_3$ Trichloro-λ^4-sulfanyl

Table 1. Acceptable substituents, which are only cited as prefixes in nodal nomenclature when the parent element is carbon.

Substituent	Prefix	IUPAC Rule [5]	Substituent	Prefix	IUPAC Rule [5]
$-F$	Fluoro	C-102.1	$-SCl_3$	Trichlorothio [*]	C-621.2
$-Cl$	Chloro	C-102.1	$-S(O)NH_2$	Sulfinamoyl	C-641.8(b)
$-ClH^+$	Chloronio	C-82.1	$-S(O)_2NH_2$	Sulfonamoyl	C-641.8(b)
$-ClO$	Chlorosyl	C-106.2	$-SNH_2$	Sulfenamoyl	C-641.8(b)
$-ClO_2$	Chloryl	C-106.2	$-SCN$	Thiocyanato [**]	C-833.1
$-ClO_3$	Perchloryl	C-106.2	$=Se$	Selenoxo	C-701.1
$-Br$	Bromo	C-102.1	$-SeH_2^+$	Selenonio	C-82.1
$-BrH^+$	Bromonio	C-82.1	$-SeCN$	Selenocyanato [**]	C-833.1
$-I$	Iodo	C-102.1	$\equiv N$	Nitrilo	
$-IH^+$	Iodonio	C-82.1	$=N_2$	Diazo	C-931.4
$-ICl_2$	Dichloroiodo [*]	C-106.3	$-N_3$	Azido	C-941.1
$-IO$	Iodosyl	C-106.1	$=NH_2^+$	Iminio	C-816.3
$-IO_2$	Iodyl	C-106.1	$-NH_3^+$	Ammonio	C-82.1; C-816.3
$-I(OH)_2$	Dihydroxyiodo [*]	C-106.3	$-NHOH$	Hydroxyamino	C-841.1
$=O$	Oxo	C-311.1	$-NHNH_2$	Hydrazino	C-921.1(b)
$-OH_2^+$	Oxonio	C-82.1	$-NO$	Nitroso	C-851.1
$-OOH$	Hydroperoxy	C-218.1(b)	$-NO_2$	Nitro	C-852.1
$-ONH_2$	Aminooxy	C-841.2(d)	$=NOH$	Hydroxyimino	C-842.1(b)
$-OCN$	Cyanato [**]	C-833.1	$-N(O)OH$	*aci*-Nitro	C-852.2
$=S$	Thioxo	C-532.3	$=NNH_2$	Hydrazono	C-922.1(b)
$-SH_2^+$	Sulfonio	C-82.1	$-NC$	Isocyano [**]	C-833.1
$-SF_5$	Pentafluorothio [*]	C-621.2	$-NCO$	Isocyanato [**]	C-833.1
$-SF_2Cl$	Chlorodifluorothio [*]	C-621.2	$-NCS$	Isothiocyanato [**]	C-833.1
$-SCl$	Chlorothio	C-621.2	$-NCSe$	Isoselenocyanato [**]	C-833.1

[*] These substituents can also be named according to **Rule N-10.3**. [**] Exception to the rule according to which, in organic nodal nomenclature, the parent hydride should contain all the carbon atoms present in the molecule. The use of the carbon-containing substituent cyano (—CN), which is generally linked to the parent hydride by a C—C bond, is not recommended.

N-10.4. The prefixes for anionic substituents formed by loss of a proton from the substituent groups listed in Table 2 are obtained by making the following changes in the names given in the second column of Table 2:

(1a) "-o" to "-onato";
(1b) "-o" to "-ato";
(1c) "Hydroxy" to "Oxido";
(1d) "Mercapto" to "Sulfido";
(1e) "Hydroseleno" to "Selenido".

The suffixes for anionic substituents formed by loss of a proton from the substituent groups listed in Table 2 are obtained by making the following changes in the names given in the third column of Table 2:

(2a) "-ic acid" to "-ate";
(2b) "-ol" to "-olate";
(2c) "-ine" to "-inide".

Anionic substituents have priority for citation as principal substituents over all other substituents. Among anionic

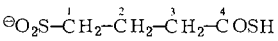
Table 2. Acceptable Substituents, which can also be cited as suffixes in nodal nomenclature when the parent element is carbon. (In descending order of priority for citation as principal substituent, cf. **Rule N-14.1**.)

Substituent	Prefix [**]	Suffix [**]	IUPAC Rule [5]
$-$[C](O)OH	[*]	-oic acid (2a)	C-11.1; C-401.1
$-$[C](O)SH	[*]	-thio *S*-acid (2a)	C-541.1
$-$[C](S)OH	[*]	-thio *O*-acid (2a)	C-541.1
$-$[C](S)SH	[*]	-dithioic acid (2a)	C-541.1
$-S(O)_2OH$	Sulfo (1a)	-sulfonic acid (2a)	C-641.4
$-S(O)_2SH$	*SH*-Thiosulfo (1a)	-thiosulfonic *S*-acid (2a)	C-641.3; C-641.4
$-S(O)(S)OH$	*OH*-Thiosulfo (1a)	-thiosulfonic *O*-acid (2a)	C-641.3; C-641.4
$-S(O)(S)SH$	*SH*-Dithiosulfo (1a)	-dithiosulfonic *S*-acid (2a)	C-641.3; C-641.4
$-S(S)_2OH$	*OH*-Dithiosulfo (1a)	-dithiosulfonic *O*-acid (2a)	C-641.3; C-641.4
$-S(S)_2SH$	Trithiosulfo (1a)	-trithiosulfonic acid (2a)	C-641.3
$-S(O)OH$	Sulfino (1b)	-sulfinic acid (2a)	C-641.2
$-S(O)SH$	*SH*-Thiosulfino (1b)	-thiosulfinic *S*-acid (2a)	C-641.3; C-641.4
$-S(S)OH$	*OH*-Thiosulfino (1b)	-thiosulfinic *O*-acid (2a)	C-641.3; C-641.4
$-S(S)SH$	Dithiosulfino (1b)	-dithiosulfinic acid (2a)	C-641.3
$-SOH$	Sulfeno (1b)	-sulfenic acid (2a)	C-641.2
$-Se(O)_2OH$	Selenono (1b)	-selenonic acid (2a)	C-701.1
$-Se(O)OH$	Selenino (1b)	-seleninic acid (2a)	C-701.1
$-SeOH$	Seleneno (1b)	-selenenic acid (2a)	C-701.1
$-OH$	Hydroxy (1c)	-ol (2b)	C-201.1; C-201.2; C-202.1
$-SH$	Mercapto (1d)	-thiol (2b)	C-511.1
$-SeH$	Hydroseleno (1e)	-selenol (2b)	C-701.1
$-NH_2$	Amino	-amine (2c)	C-811.3; C-11.42
$=NH$	Imino	-imine (2c)	C-815.3(a)

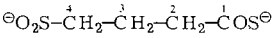
[*] When the parent element is carbon, composite substituents are named as prefixes: for instance, $-$[C](O)SH is named "(mercapto, oxo)". [**] (1a) to (1e) and (2a) to (2c): For naming the anionic substituents derived from these groups, as prefixes or as suffixes, see correspondingly numbered instructions in **Rule N-10.4**.

substituents, the priority order is the one adopted for the corresponding nonionized substituent groups.

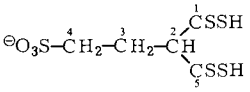
Examples (for numbering, refer to **Rules N-14.3** and **N-14.5**):

1. 

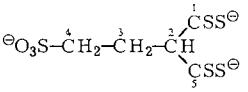
4-(Mercapto, oxo)[4]tetrane-1-sulfinate

2. 

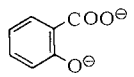
4-Sulfinato[4]tetrane-1-thioate

3. 

1,5-Bis(mercapto, thioxo)[4.1^2]pentane-4-sulfonate

4. 

4-Sulfonato[4.1^2]pentane-1,5-bis(dithioate)

5. 

2-Oxidocyclo[(06)1 : 7(1)]heptan(1-6)aren-7-oate

(For the name of the parent hydride in Example 5, see **Rule N-12.3**.)

Rule N-11—Saturated Parent Hydrides

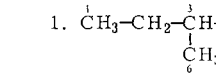
N-11.1. Names and bonding numbers for standard mononuclear element hydrides are given in Table 3. Higher homologues of these element hydrides are named by replacing, in the name of the structure graph, the ending "-nodane" by the name of the corresponding mononuclear element hydride given in Table 3.

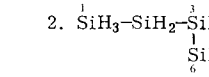
Table 3. Standard bonding numbers (SBN), names for mononuclear element hydrides and prefixes for elements in replacement nomenclature [5d].

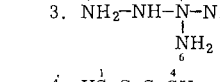
Element		Element Hydride		Replacement
Name	SBN	Formula	Name	Prefix
Fluorine	1	FH	Fluorane [a]	Fluora [a]
Chlorine	1	ClH	Chlorane [a]	Chlora [a]
Bromine	1	BrH	Bromane [a]	Broma [a]
Iodine	1	IH	Iodane [a]	Ioda [a]
Astatine	1	AtH	Astatane [a]	Astata [a]
Oxygen	2	OH_2	Oxidane [b]	Oxa
Sulfur	2	SH_2	Sulfane	Thia
Selenium	2	SeH_2	Selane	Selena
Tellurium	2	TeH_2	Tellane	Tellura
Polonium	2	PoH_2	Polane	Polona
Nitrogen	3	NH_3	Azane	Aza
Phosphorus	3	PH_3	Phosphane	Phospha
Arsenic	3	AsH_3	Arsane	Arsa
Antimony	3	SbH_3	Stibane	Stiba
Bismuth	3	BiH_3	Bismuthane	Bisma
Carbon	4	CH_4	Carbane [c]	Carba
Silicon	4	SiH_4	Silane	Sila
Germanium	4	GeH_4	Germane	Germa
Tin	4	SnH_4	Stannane	Stanna
Lead	4	PbH_4	Plumbane	Plumba
Boron	3	BH_3	Borane	Bora

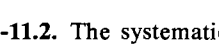
[a] These names are needed for bonding numbers other than standard (see **Rules N-10.3** and **N-14.1**). [b] "Oxidane" is preferred to "oxane" in order to avoid confusion with Hantzsch-Widman names. [c] For the choice of carbon as parent element, see particular dispositions of **Rules N-11.2** and **N-11.3**.

Examples:

1.  [5.1^3]Hexacarbane

2.  [5.1^3]Hexasilane

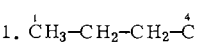
3.  [5.1^3]Hexaazane

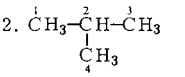
4.  [4]Tetrasulfane

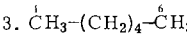
N-11.2. The systematic names of the higher hydrocarbons are so well known in organic chemistry that the morpheme "carb" can be elided where there is no risk of ambiguity. When a molecule of a saturated hydrocarbon contains less than four carbon atoms, the descriptor is not necessary and the trivial names (*i.e.*, methane, ethane, propane, and cyclopropane) are so firmly entrenched that they can be used as exceptions instead of the systematic names (*i.e.*, [1]carbane, [2]dicarbane, [3]tricarbane, and cyclo[03]tricarbane, respectively). However, the systematic names [4]tetracarbane (or [4]tetrane) and [3.1^2]tetracarbane (or [3.1^2]tetrane) are preferred to the trivial butane and isobutane names because use of the descriptor is necessary to distinguish between the isomers and to define the numbering of the skeleton.

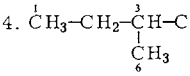
Examples (IUPAC names[5e] are given in parentheses for comparison):

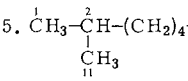
a) Saturated acyclic hydrocarbons

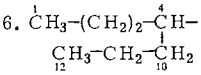
1.  [4]Tetrane [*] (Butane)

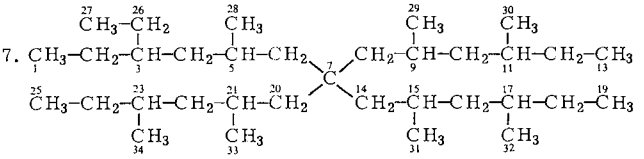
2.  [3.1^2]Tetrane (Isobutane)

3.  [6]Hexane (Hexane)

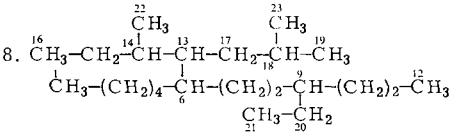
4.  [5.1^3]Hexane (3-Methylpentane)

5.  [10.1^{2}1^{7}1^8]Tridecane (2,7,8-Trimethyldecane)

6.  [9.3^{4}1^5]Tridecane (5-Methyl-4-propylnonane)

7. 

[13.6^{7}6^{7}2^{3}1^{5}1^{9}1^{11}1^{15}1^{17}1^{21}1^{23}]Tetratriacontane (7,7-Bis(2,4-dimethylhexyl)-3-ethyl-5,9,11-trimethyltridecane)

8. 

[12.4^{6}3^{13}2^{9}1^{14}1^{18}]Tricosane (4-Ethyl-7-(1-isobutyl-2-methylbutyl)dodecane)

[*] In this and subsequent examples, the morpheme "carb" is elided.

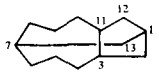
b) Saturated cyclic hydrocarbons

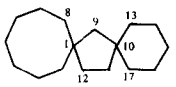
9. Cyclopropane

10. Cyclo[06]hexane
(Cyclohexane)

11. Bicyclo[04.0^{1,3}]tetrane
(Bicyclo[1.1.0]butane)

12. Bicyclo[07.1^{1,4}]octane
(Bicyclo[3.2.1]octane)

13.  Tricyclo[012.1^{1,7}0^{3,11}]tridecane
(Tricyclo[5.5.1.0^{3,11}]tridecane)
(Perhydo-2,7-methanocyclopenta-cyclononene)

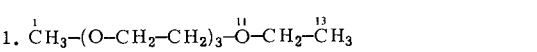
14.  Tricyclo[08.4^{1,1}5^{10,10}]heptadecane
(Dispiro[5.1.7.2]heptadecane)

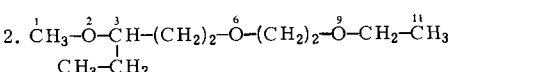
N-11.3. Heteroatomic hydrides containing atoms of more than one element other than hydrogen are named by replacement nomenclature[5b,f]. Such a structure is first named as though the skeleton contains only the parent element, *i.e.* the most common element other than hydrogen. Atoms of less common elements are then named by means of the prefixes in Table 3, in the order given, with locants to indicate their positions. When a skeleton contains equal numbers of atoms of more than one element, including carbon, carbon is preferred as the parent element. If carbon is not among the most common elements of the skeleton, the parent element is the first cited in Table 3.

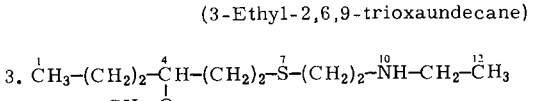
If Part I leaves a choice, lowest locants are assigned first to heteroatoms as a complete set, then to heteroatoms in the order of Table 3.

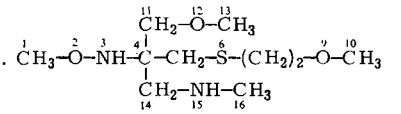
Examples (IUPAC names[5b,f] are given in parentheses for comparison):

a) Saturated acyclic heteroatomic compounds

1. 
2,5,8,11-Tetraoxa[13]tridecane
(2,5,8,11-Tetraoxatridecane)

2. 
2,6,9-Trioxa[11.2^3]tridecane
(3-Ethyl-2,6,9-trioxaundecane)

3. 
13-Oxa-7-thia-10-aza[12.2^4]tetradecane
(3-Propyl-2-oxa-6-thia-9-azaundecane)

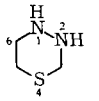

4.
2,9,12-Trioxa-6-thia-3,15-diaza[10.3^{4}3^4]hexadecane
(4-(Methoxymethyl)-4-[(methylamino)methyl]-2,9-dioxa-6-thia-3-azadecane)

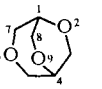
b) Saturated cyclic heteroatomic compounds

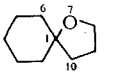
5. 1-Oxacyclopropane
(Oxirane)

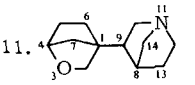
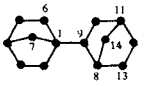
6. 1-Azacyclopropane
(Aziridine)

7. 1-Oxa-2-thiacyclo[05]pentane
(1,2-Oxathiolane)

8.  4-Thia-1,2-diazacyclo[06]hexane
(1-Thia-3,4-diazinane)
(1-Thia-3,4-diazacyclohexane)

9.  2,6,9-Trioxabicyclo[07.2^{1,4}]nonane
(3,6,8-Trioxabicyclo[3.2.2]nonane)

10.  7-Oxabicyclo[06.4^{1,1}]decane
(1-Oxaspiro[4.5]decane)

11.  from: 

3-Oxa-11-azatetracyclo-[(06.1^{1,4})1 : 9(06.1^{1,4})]tetradecane
(3-(2-Oxabicyclo[2.2.1]hept-4-yl)-1-azabicyclo[2.2.1]heptane)

Tetracyclo[(06.1^{1,4})1 : 9-(06.1^{1,4})]tetradecanodane

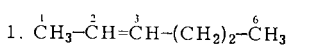
Rule N-12—Unsaturated Parent Hydrides: Names Derived from those of Saturated Structures

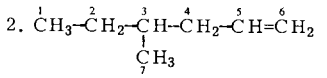
N-12.1. *Double* and *triple bonds* are indicated by the usual suffixes, *i.e.*, "-ene", "-diene", "-yne", "-diyne", "en...yne", *etc.* In contrast with present usage, the ending "-ane" of the corresponding saturated structure is maintained in the name of the unsaturated compounds, with elision of the final "e" before the vowels "e" or "y"[8]. Locants of two atoms linked by a multiple bond are placed immediately before the appropriate suffix and are cited in ascending order, with the second locant enclosed in parentheses. The second locant is omitted when it exceeds the first by unity. As far as Part I and Rule **N-11.3** leave a choice, lowest locants are assigned first to double and triple bonds as a complete set, even though this may, at times, give "yne" a lower locant than "ene". When there remains a choice, lowest locants are assigned to double bonds.

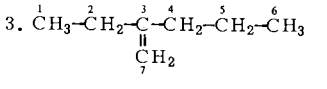
For the reasons given in **Rule N-11.2**, the IUPAC systematic names "ethene", "ethyne", "propene", "cyclopropene", "propadiene" and "propyne" are retained.

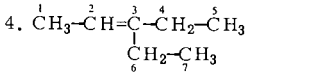
Examples (IUPAC names are given in parentheses for comparison):

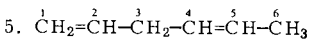
a) Unsaturated acyclic hydrocarbons[5e]

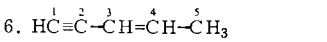
1.  [6]Hexan-2-ene (2-Hexene)

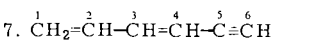
2.  [6.1^3]Heptan-5-ene (4-Methyl-1-hexene)

3.  [6.1^3]Heptan-3(7)-ene (2-Ethyl-1-pentene)

4.  [5.2^3]Heptan-2-ene (3-Ethyl-2-pentene)

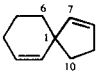
5.  [6]Hexane-1,4-diene (1,4-Hexadiene)

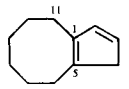
6.  [5]Pentan-3-en-1-yne (3-Penten-1-yne)

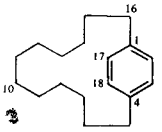
7.  [6]Hexane-1,3-dien-5-yne (1,3-Hexadien-5-yne)

b) Unsaturated cyclic hydrocarbons[5e]

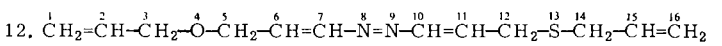
8. Cyclo[06]hexanene (Cyclohexene)

9.  Bicyclo[06.4^{1,1}]decane-2,7-diene (Spiro[4.5]deca-1,6-diene)

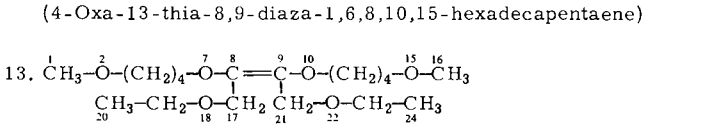
10.  Bicyclo[011.0^{1,5}]undecane-1(5),2-diene (4,5,6,7,8,9-Hexahydro-1*H*-cyclopentacyclooctene)

11.  Bicyclo[016.2^{1,4}]octadecane-1,3,17-triene (Bicyclo[12.2.2]octadeca-1(16),14,17-triene)

c) Unsaturated acyclic heteroatomic compounds[5b]

12. 

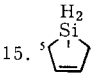
4-Oxa-13-thia-8,9-diaza[16]hexadecane-1,6,8,10,15-pentaene (4-Oxa-13-thia-8,9-diaza-1,6,8,10,15-hexadecapentaene)

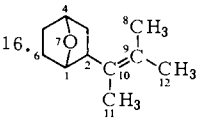
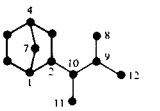
13. 

2,7,10,15,18,22-Hexaoxa[16.4^{8}4^9]tetracosan-8-ene (8,9-Bis(ethoxymethyl)-2,7,10,15-tetraoxa-8-hexadecene)

d) Unsaturated cyclic heteroatomic compounds[5c]

14. 1-Aza-2-arsacyclo[04]tetran-3-ene (1,2-Dihydro-1,2-azarsete) (or 3,4-Didehydro-1,2-azarsetidine)

15.  1-Silacyclo[05]pentan-3-ene (2,5-Dihydro-1*H*-silole) (or 3,4-Didehydrosilolane)

16.  from: 

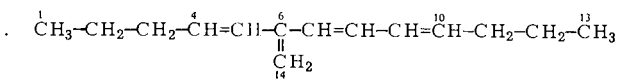
7-Oxabicyclo[(06.1^{1,4})2:10(4.1^2)]-dodecan-9-ene (2-(1,2-Dimethyl-1-propenyl)-7-oxabicyclo[2.2.1]heptane)

Bicyclo-[(06.1^{1,4})2:10(4.1^2)]-dodecanodane

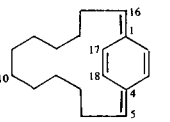
N-12.2. The presence in a more complex hydride of a part containing the maximum number of noncumulative double bonds is indicated by the suffix "axene" added to the name of the saturated hydride, with elision of the latter's terminal "e". This procedure is applied when the part structure contains at least three noncumulative double bonds.

The position of unsaturation is indicated by locants, preceding the suffix "axene" and describing *all* the skeletal atoms present in the part(s) of the structure concerned. A group of locants such as (1—6) means that all the atoms numbered from 1 to 6 inclusively belong to a part of the compound containing the maximum number of noncumulative double bonds. More than one set of locants may be associated with the suffix "-axene".

Examples:

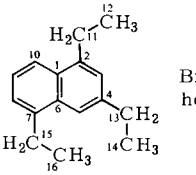
1. 

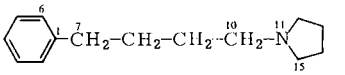
[13.1^6]Tetradecan(4-10,14)axene

2.  Bicyclo[016.2^{1,4}]octadecan(1-5,16-18)axene

N-12.3. If the aromatic character of the part containing the maximum number of noncumulative double bonds is to be stressed, the suffix "axene" can be replaced by "arene".

Examples:

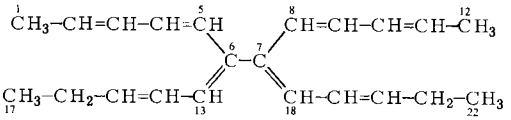
1.  Bicyclo[(010.0^{1,6})2:11(2)4:13(2)7:15(2)]-hexadecan(1-10)arene

2. 

11-Azabicyclo[(06)1:7(4)10:11(05)]pentadecan(1-6)arene

N-12.4. If there is a choice, the locants of the "axene" or "arene" suffixes should be as low as possible. All the locants of the atoms belonging to the part with the maximum number of noncumulative double bonds are then considered as one set notwithstanding the fact that some may be explicitly cited while others are implicit, such as 3,4,5,6,7,8,9,10 in (2—11) in the following example.

Example:



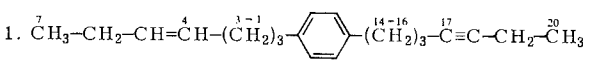
[12.5^{6}5^7]Docosan(2-11,13-15,18-20)axene

(NOT: (2—10, 13—15, 18—21), because 2...10, 11, 13... is lower than 2...10, 13, 14...)

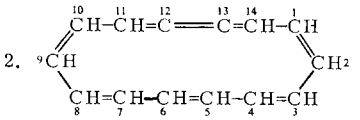
N-12.5. When a part of a structure contains the maximum number of noncumulative double bonds while other parts contain either isolated or cumulative double bonds and/or triple bonds, the corresponding suffixes are cited in the order: "-axene" (or "-arene"), "-ene", "-yne". Locants of cumulative and isolated double bonds are cited together when the "-axene" ending is used.

If there is a choice, lowest possible locants are first assigned to the atoms concerning the "-axene" (or "-arene") term, as defined in **Rule N-12.4**; afterwards, if there remains a choice, lowest possible locants are assigned to explicitly cited multiple bonds (double and triple bonds considered together). If there is still a choice, lowest possible locants are assigned to double bonds. This is the pattern set by IUPAC **Rule A-3.3**.

Examples:

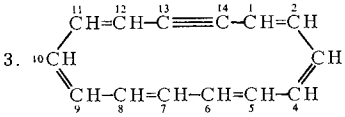
1. 

Cyclo[(7)1:8(06)11:14(7)]icosan(8-13)aren-4-en-17-yne

2. 

Cyclo[014]tetradecan-(1-10)axene-11,12,13-triene

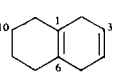
(NOT...(5—14)axene-1,2,3-triene, since the suffix "-axene" claims the lowest locants.)

3. 

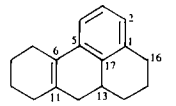
Cyclo[014]tetradecan-(1-12)axen-13-yne

N-12.6. When, in an "*ortho*-fused" or "*ortho*- and *peri*-fused" polycyclic ring system, the number of double bonds is equal to, or smaller than, two-thirds of the maximum number of noncumulative double bonds, the name is formed from the name of the corresponding saturated ring system *by adding to the ending "ane"* the appropriate "ene", "axene", or "arene" suffixes (see **Rules N-12.1, N-12.2** and **N-12.3**) and associated locant(s).

Examples:

1. 

Bicyclo[010.0^{1,6}]decane-1(6),3-diene (1,2,3,4,5,8-Hexahydronaphthalene)

2.  or

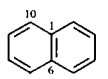
Tetracyclo[016.1^{1,5}0^{6,11}0^{13,17}]-heptadecane-1,3,5(17),6(11)-tetraen
Tetracyclo[016.1^{1,5}0^{6,11}0^{13,17}]-heptadecan(1-6,11,17)axene (5,6,6a,7,8,9,10,11-Octahydro-4*H*-benz[*de*]anthracene)

Rule N-13—Unsaturated Parent Hydrides: Names Derived from those of Structures having the Maximum Number of Noncumulative Double Bonds (Partly alternative to Rule N-12)

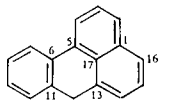
N-13.1. The name of an unsaturated hydride containing the maximum number of noncumulative double bonds is obtained by *replacing,* in the name of the corresponding saturated hydride, *the ending "ane" by the suffix "axene".* If the aromatic character of the hydride is to be indicated, the suffix "arene" is used instead of "axene".

The presence of at least one hydrogen atom on a skeletal atom joined to adjacent skeletal atoms by only single bonds is denoted by "indicated hydrogen"[9].

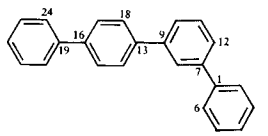
Examples:

1. 

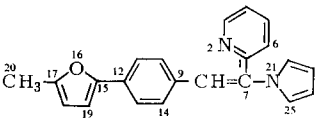
Bicyclo[010.0^{1,6}]decarene (Naphthalene)

2. 

12*H*-Tetracyclo[016.1^{1,5}0^{6,11}0^{13,17}]-heptadecarene (7*H*-Benz[*de*]anthracene)

3. 

Tetracyclo[(06)1:7(06)9:13(06)16:19(06)]tetracosarene

4. 

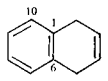
20*H*-16-Oxa-2,21-diazatetracyclo-[(06)1:7(2)8:9(06)12:15(05)17:20(1)7:21(05)]-pentacosaxene

N-13.2. An unsaturated hydride containing a number of double bonds less than the maximum number of noncumulative double bonds, but larger than two-thirds of this number, can be named by adding a prefix "dihydro", "tetrahydro", *etc.,* to the name of the corresponding hydride having the maximum number of noncumulative double bonds.

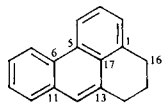
Indicated hydrogen has priority over "hydro" prefixes for assignment of lowest possible locants. For this pur-

pose, a structure with the maximum number of noncumulative double bonds, having the lowest possible locant(s) for indicated hydrogen(s) is first selected. Only then, are lowest possible locants assigned to hydro prefixes. This method implies that, eventually, an indicated hydrogen locant may be higher than a hydro locant (see example 4).

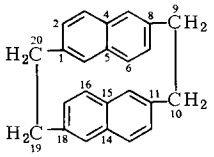
Examples:

1. 

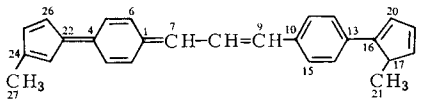
2,5-Dihydrobicyclo[010.0^{1,6}]decarene
(1,4-Dihydronaphthalene)

2. 

15,16-Dihydro-14*H*-tetracyclo-
[016.1^{1,5}0^{6,11}0^{13,17}]heptadecarene
(5,6-Dihydro-4*H*-benz[*de*]anthracene)

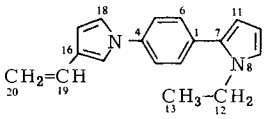
3. 

9,10,19,20-Tetrahydropentacyclo-
[020.1^{1,5}1^{4,8}1^{11,15}1^{14,18}]tetracosaxene

4. 

17,27-Dihydro-21*H*-tetracyclo-
[(06)1 : 7(3)9 : 10(06)13 : 16(05)17 : 21(1)4 : 22(05)24 : 27(1)]-
heptacosaxene

(Only 21*H* and 27*H* correspond to canonical structures having the maximum number of noncumulative double bonds; no 17*H* structure exists.)

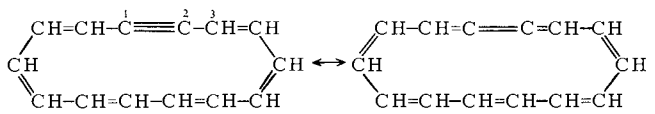
5. 

12,13-Dihydro-8,14-diazatricyclo-
[(06)1 : 7(05)8 : 12(2)4 : 14(05)16 : 19(2)]icosaxene

N-13.3. When a parent hydride corresponds to a loss of hydrogen from a structure having the maximum number of noncumulative double bonds, it can be named by adding a prefix such as "didehydro", "tetradehydro", *etc.*, with appropriate locants, to the name of the corresponding hydride having the maximum number of noncumulative double bonds.

It is recommended that the "hydro" and "dehydro" prefixes not be used simultaneously in the same name. Structures for which this circumstance would happen should be named according to **Rule N-12**. For assignment of lowest possible locants, "dehydro" prefixes immediately follow indicated hydrogen.

Example (to be compared with examples 2 and 3 of **Rule N-12.5**):



1,2-Didehydrocyclo[014]tetradecaxene

Rule N-14—Construction of the Name

N-14.1. The various parts of the name occur in the following order:

a) Substituent prefixes, in alphabetical order;
b) Name of the neutral parent hydride, comprising:
   1) Dehydro and hydro prefixes;
   2) Indicated hydrogen;
   3) Replacement prefixes ("a" prefixes), in the same order as in Table 3;
   4) Name of the structure graph in which "nodane" is replaced by an affix denoting the parent element (**Rule N-11**);
   5) Endings indicating unsaturation ("-ene", "-yne", "-axene" or "-arene").
c) *EITHER* One or several ionic and/or free valence suffix(es), in the order: "-ium", "-ylium", "-ide", suffix for anionic principal substituent (**Rule N-10.4**), "-yl";
   OR A suffix denoting a neutral principal substituent (**Rule N-10.2**).

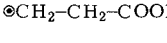
Suffixes denoting free valences ("-yl", "-diyl", *etc.*) are always cited at the end of the name. They preclude the simultaneous presence of a suffix denoting a neutral principal substituent. In nodal nomenclature, these suffixes are used exclusively for free radicals or for substituents which do not need internal numbering (*e.g.*, **Rule N-10.3**: Dichloro-λ^3-iodanyl).

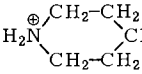
Anionic principal substituents defined in **Rule N-10.4** may be cited after the other ionic suffixes. If there is more than one kind of anionic substituent, **Rule N-10.4** determines the anionic substituent to be cited as a suffix. Other anionic substituents are then denoted by the prefix(es) given in **Rule N-10.3**.

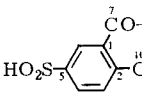
Only one kind of neutral substituent group can be denoted by a suffix (principal substituent). When there is a choice, the principal substituent is the first cited in Table 2. If substituents other than those cited in this table are used, their order of priority is defined by pertinent IUPAC Rules such as **C-10.4**, **C-641.2**, **D-1.31**, **D-1.32**, and **D-1.33**[5].

Atoms or groups which cannot be denoted as a substituent by a suffix or a prefix are expressed as part of the neutral parent hydride.

Examples:

1.  3-(Hydroxy,oxo)propan-1-yl

2.  4-Azacyclo[(06)1 : 7(1)]heptan-4-ium-7-oate

3.  7-Oxo-5-sulfino-8-oxacyclo-[(06)1 : 7(3)2 : 10(1)]decan(1-6)-aren-10-oic acid

(According to Table 2, (C)OOH is preferred to SO_3H as principal substituent.)

N-14.2. According to Part I[2] and to the preceding Rules, the numbering of any structure is determined by the

following criteria, applied successively until a decision is reached:

a) Criteria given in Part I concerning the numbering of the structure graph;
b) Lowest locants for replacement prefixes considered together (**Rule N-11.3**);
c) Lowest locants for replacement prefixes considered in the order of Table 3 (**Rule N-11.3**).

Depending on whether **Rule N-12** or **Rule N-13** is used for indicating unsaturation, locants are then assigned to unsaturation affixes in one of the two following ways:

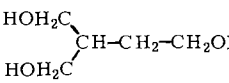
(**Rule N-12**)—In names derived from those of saturated structures, lowest locants are assigned to:

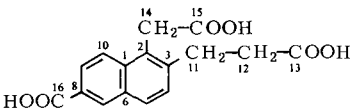
d_1) "-axene" or "-arene" suffixes (**Rules N-12.4** and **12.5**);
e_1) Explicitly cited multiple bonds as a complete set, then double bonds (**Rules N-12.1** and **12.5**).

(**Rule N-13**)—In names derived from those of structures having the maximum number of noncumulative double bonds, lowest locants are assigned to:

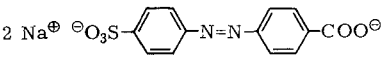
d_2) Indicated hydrogen (**Rules N-13.1** and **N-13.2**);
e_2) "Hydro" or "dehydro" prefixes (**Rules N-13.2** and **N-13.3**), it being understood that these two types of prefixes do not coexist in the same name.

Examples (decisive criteria are indicated within parentheses):

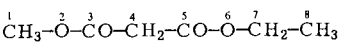
1. (a)  [4.1²]Pentane-1,4,5-triol (2-(Hydroxymethyl)-1,4-butanediol)

2. (a) 

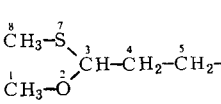
Bicyclo[(010.0^{1,6})3:11(3)2:14(2)8:16(1)]hexadecan-(1-10)arene-13,15,16-trioic acid
(6-Carboxy-1-(carboxymethyl)-2-naphthalenepropionic acid)

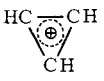
3. (a) 

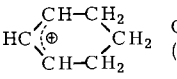
Disodium 4-sulfonato-7,8-diaza-15*H*-bicyclo-[(06)1:7(2)8:9(06)12:15(1)]pentadecaxen-15-oate
(Disodium 4'-sulfonatoazobenzene-4-carboxylate or: Disodium *p*-(*p*-sulfonatophenylazo)benzoate)

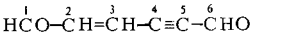
4. (b) 

3,5-Dioxo-2,6-dioxa[8]octane
(Ethyl methyl malonate)

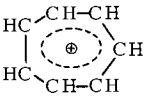
5. (c)  2-Oxa-7-thia[6.2³]octane (1-Methoxy-1-(methylthio)butane)

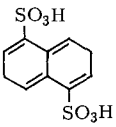
6. (e_1)  Cycloprop-1-en-3-ylium (2-Cyclopropen-1-ylium) [*]

7. (e_1)  Cyclo[06]hexan-1-en-3-ylium (2-Cyclohexen-1-ylium) [*]

8. (e_1) 

1,6-Dioxo[6]hexan-2-en-4-yne
(2-Hexen-4-ynedial)

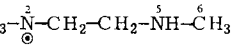
9. (d_2)  1*H*-Cyclo[07]heptaxen-1-ylium (2,4,6-Cycloheptatrien-1-ylium)

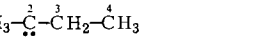
10. (e_2)  3,8-Dihydrobicyclo[010.0^{1,6}]-decarene-5,10-disulfonic acid (3,7-Dihydronaphthalene-1,5-disulfonic acid)

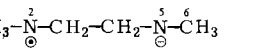
N-14.3. When Part I and **Rule N-14.2** leave a choice for the numbering of the skeleton of a chemical structure, the following criteria are applied successively until a decision is reached, giving the lowest locant to:

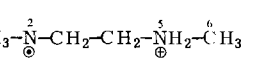
a) Free valences, denoted by the suffix "-yl";
b) Anionic skeletal atoms denoted by the suffix "-ide";
c) Cationic skeletal atoms denoted by the suffix "-ylium", corresponding to the loss of an electron at a free valence position;
d) Cationic skeletal atoms denoted by the suffix "-ium", corresponding to the fixation of a proton;
e) Anionic substituents named by a suffix (see **Rule N-10.4**);
f) Anionic substituents named by a prefix (see **Rule N-10.4**);
g) Cationic substituents named by a prefix (see Table 1).

Examples (decisive criteria are indicated within parentheses):

1. (a)  2,5-Diaza[6]hexan-2-yl

2. (a)  [4]Tetrane-2,2-diyl

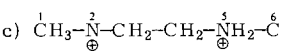
3. (a)  2,5-Diaza[6]hexan-5-id-2-yl

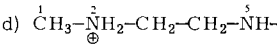
4. (a)  2,5-Diaza[6]hexan-5-ium-2-yl

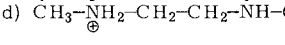
5. (b) 2,5-Diaza[6]hexan-2-ide

6. (c) [4]Tetran-2-ylium

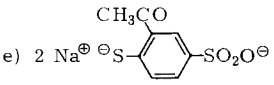
[*] As in classical organic nomenclature, free radicals with delocalized free valences, or ions with delocalized charges, can be named by arbitrarily selecting a localized form, *e.g.*, 2-cyclohexen-1-ylium (**Rule C-83.1** [5]). When this procedure is used in nodal nomenclature, it is important to note that the numbering of the neutral parent hydride, including unsaturation, has priority over ionic charges for low locants. This arbitrary numbering may therefore be different from the arbitrary numbering recommended by IUPAC Rules (see examples 6 and 7). Pending publication of IUPAC Rules on delocalized ions and radicals, no attempt to treat this subject is made here.

7. (c)  2,5-Diaza[6]hexan-5-ium-2-ylium

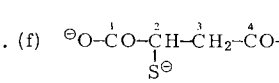
8. (d)  2,5-Diaza[6]hexan-2-ium

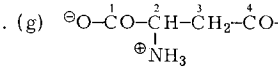
9. (d)  6-(Oxido,oxo)-2,5-diaza-[6]hexan-2-ium

(Ionic skeletal atoms having priority for low locants over ionic substituents, it is preferable to use prefixes for the latter.)

10. (e)  Disodium 7-oxo-6-sulfidocyclo-[(06)1 : 7(2)]octan(1-6)arene-3-sulfonate

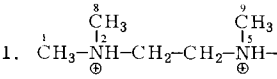
(The principal substituent SO_3^- has the locant 3, not 5.)

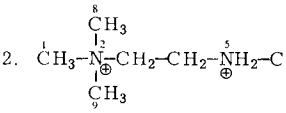
11. (f)  2-Sulfido[4]tetrane-1,4-dioate

12. (g)  2-Ammonio[4]tetrane-1,4-dioate

N-14.4. The description of the skeleton is completed before considering the distribution of hydrogen atoms and of ionic charges. Therefore, a cationic skeletal atom may be denoted by the *suffix* "ium" only if it bears at least one hydrogen atom. If this is not the case, the *suffix* "ylium" is used, associated with the indication of a nonstandard bonding number by a "λ^n" symbol[7].

Examples:

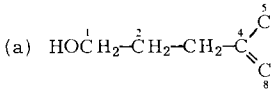
1.  2,5-Diaza[7.1^{2}1^5]nonan-2,5-diium

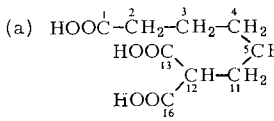
2.  2λ^5,5-Diaza[7.1^{2}1^2]-nonan-5-ium-2-ylium

N-14.5. When the preceding rules leave a choice for the numbering of the skeleton of a chemical structure, the following criteria are applied successively until a choice is made, giving lowest locants to:

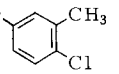
a) Neutral principal substituent, denoted by a suffix;
b) Neutral substituents denoted by prefixes, considered together;
c) Neutral substituents denoted by prefixes, in alphabetical order.

Examples (decisive criteria are indicated within parentheses):

1. (a)  [7.2^4]Nonan-4(8)-en-1-ol (4-Propyl-4-hex-en-1-ol)

2. (a) 

[10.3^{5}1^{8}1^{9}1^{12}]Hexadecane-1,10,13,14,16-pentoic acid (3-(3-Carboxypropyl)-1,1,6,7-octanetetracarboxylic acid)

3. (b)  5-Bromo-2-chlorocyclo-[(06)1 : 7(1)]heptan(1-6)arene

4. (c) $N{\equiv}C{-}CH_2{-}CO{-}CH_2{-}CHO$ 1-Nitrilo-3,5-dioxo[5]pentane (4-Formyl-3-oxobutanenitrile)

6. Conclusion

We have shown that the use of nodal nomenclature (with its structure graphs, mathematical description of chemical structures, unique and sequential numbering, and virtual equivalence of substituents with characteristic groups) simplifies the naming of chemical substances, particularly organic compounds with complex structures. The resulting names are not fragmented and are based upon a single numbering sequence, avoiding the scattering in the name of substitutive affixes and replacement terms.

The present work giving only rather general suggestions for adapting the substitutive method to nodal nomenclature, a more extensive and more detailed treatment of functional groups may deserve a further study. We consider also the extension of nodal nomenclature to other types of chemical substances such as polynuclear coordination compounds.

The Authors wish to thank members of the IUPAC Commission on Nomenclature of Organic Chemistry for their comments and, in particular, Prof. D. Hellwinkel for translating this paper into German.

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German version: *Angew. Chem. 96* (1984) 1

Note on Part I[2]

Examination of **Rules N-5.3** to **N-5.34** inclusive showed that their selection criteria for numbering and naming assemblies could be simplified and made more exhaustive. The following Rules, denoted **RN-5.3** to **RN-5.34** have therefore been devised in order to replace the preceding **Rules N-5.3** to **N-5.34**.

This new text reproduces many features of the preceding one (including note[23]), sometimes in a different order, and does not affect the name of any example in the original paper.

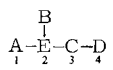
RN-5.3. *Numbering of the module seniority graph, i.e.* assignment of the module seniority numbers, which determines the order of assignment of the definitive sequential numbering of the assembly (see **Rule N-5.1**), begins with the principal module (see **Rule N-4.2**) and proceeds successively through each chain of contraction nodes attached to the principal module. Selection rules for numbering the module seniority graph differ from those applied to acyclic graphs (**Rule N-1**) because module seniority graphs deal with constituent units (modules) which may greatly differ in structural complexity. Accordingly, rules for the module seniority graph take into consideration the nature of the contraction nodes, while, according to **Rule N-1**, the nature of the nodes does not affect the numbering of the graph.

RN-5.31. A module seniority graph is considered as formed by one or more *unbranched chain(s) of modules* which are called *segments* and defined as follows.

RN-5.311. The numbering of a module seniority graph starts from the (one of the) senior module(s), called the *principal module* and continues sequentially according to the following procedure:

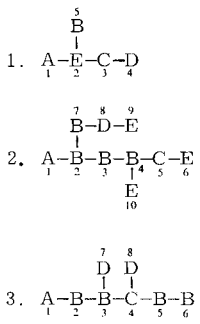
a) In a chain of modules bound to the principal module, the *main segment* is the longest (or one of the longest) attached to the principal module and is numbered sequentially after the principal module.

Example:



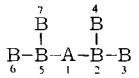
b) Other segments of a chain of modules are numbered sequentially, starting always with the (one of the) longest segment(s) bound to a module already numbered. Segments of equal length are numbered in the increasing numerical order of their locants of attachment.

Examples:



c) Any chain of modules, unbranched or branched, bound to the principal module, is entirely numbered before numbering another chain (if any) bound to the principle module.

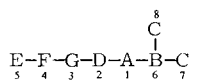
Example:



RN-5.312. When two or more chains of modules are attached to the principal module, the order in which these chains are numbered is decided by the following criteria considered successively until a decision is reached:

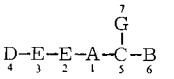
a) Largest number of modules in the entire chain.

Example:



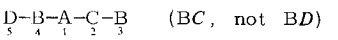
b) Longest unbranched chain of modules (*i.e.*, longest main segment).

Example:



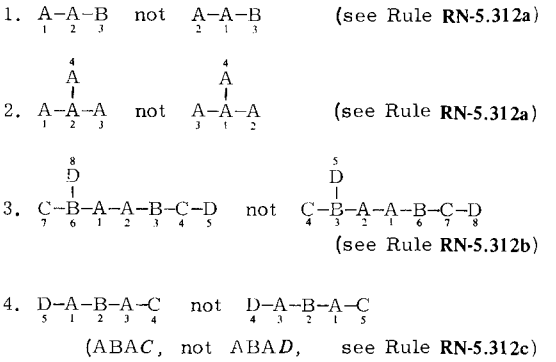
c) Senior module, at the first difference, when the various sets of modules are compared, term by term, in order of decreasing seniority as defined in **Rule N-4.2**, regardless of the positions of the modules in the chains.

Example:


(B*C*, not B*D*)

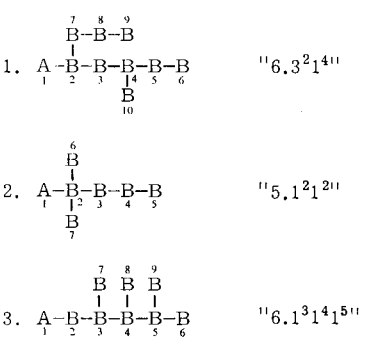
RN-5.313. When a module seniority graph contains two or more modules of highest seniority, *i.e.* with module seniority descriptor A, the *principal module* is that senior module to which is attached the most senior chain of contraction nodes when these chains are compared term by term, in order of decreasing seniority, this order being determined by the criteria described in **Rule RN-5.312**.

Examples:



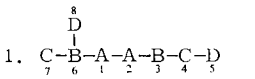
RN-5.32. The *module graph descriptor* consists of quotation marks enclosing: a) an Arabic numeral denoting the number of modules, including the principal one, in the first (main) segment to be numbered; b) a period followed by Arabic numerals denoting the number of modules in each segment, cited in their order of numbering; c) a superscript locant for each segment defined under b), denoting the module, in the part of the graph already numbered, to which the segment is attached.

Examples:

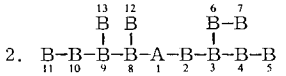


RN-5.33. When there remains a choice for the order of numbering of the chains or for the selection of the principal module, the correct numbering of the module seniority graph is the one corresponding to the module graph descriptor having the preferred numeral at the first difference: if the first difference corresponds to a segment length, the preferred numeral is higher; if the first difference appears in a superscript numeral (locant of a module), the preferred numeral is lower.

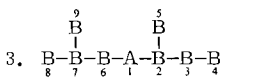
Examples:



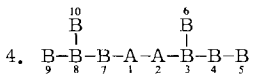
1. "$5.2^{1}1^{6}$" not "$4.1^{3}3^{1}$"



2. "$5.2^{3}4^{1}1^{8}1^{9}$" not "$5.1^{2}1^{3}4^{1}2^{9}$"



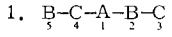
3. "$4.1^{2}3^{1}1^{7}$" not "$4.1^{3}3^{1}1^{6}$"



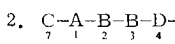
4. "$5.1^{3}3^{1}1^{8}$" not "$5.1^{4}3^{1}1^{7}$"

RN-5.34. If the preceding Rules leave a choice for the numbering, the correct numbering is the one giving the lowest locant, at the first difference, when modules are considered in order of decreasing seniority.

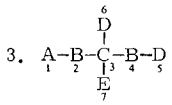
Examples:



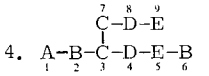
1. locants for B: 2,5 not 3,4



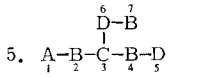
2. locants for B: 2,3 not 3,4



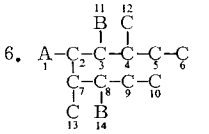
3. locants for D: 5,6 not 5,7



4. locants for B: 2,6 not 2,9



5. locants for B: 2,4,7 not 2,5,6



6. locants for B: 11,14 not 12,13

Rule **N-5.35** and following Rules unchanged.

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[1] For a detailed discussion of mathematical descriptions of chemical structures, see A. L. Goodson, Application of Graph-Based Chemical Nomenclature to Theoretical and Preparative Chemistry - IUPAC International Symposium on Theoretical Organic Chemistry, Dubrovnik 1982; *Croat. Chem. Acta 56* (1983) 315.

[2] N. Lozac'h, A. L. Goodson, W. H. Powell, *Angew. Chem. 91* (1979) 951; *Angew. Chem. Int. Ed. Engl. 18* (1979) 887; *ibid.* Section 4.

[3] A. T. Balaban: *Chemical Applications of Graph Theory,* Academic Press, London 1976.

[4] A. L. Goodson, *J. Chem. Inf. Comput. Sci. 20* (1980) 167; "Nomenclature of Chemical Compounds", in N. N. Tyutyulkov, D. Bonchev: *Graph Theory and its Application in Chemistry,* Nauka i Izkutsvo, Sofia, in press.

[5] IUPAC, Nomenclature of Organic Chemistry, Sections A, B, C, D, E, F, and H, Pergamon Press, Oxford 1979; a) *ibid.* p. 82 and Section D-0.3; b) *ibid.* Section C-0.6; c) *ibid.* **Rule B-1**; d) *ibid.* **Rule D-4.11** and Table I, p. 459; *ibid.* e) Section A; f) *ibid.* Section B.

[6] Generalization of replacement nomenclature was proposed in IUPAC Commission on Nomenclature of Organic Chemistry, Unpublished Studies toward a Structure-Based Substitutive Nomenclature, 1975–1977.

[7] IUPAC Commission on Nomenclature of Organic Chemistry, The Designation of Nonstandard Classical Valence Bonding in Organic Chemistry, *Pure Appl. Chem. 54* (1982) 217.

[8] First proposed by the IUPAC Commission on Nomenclature of Organic Chemistry Working Party for Section G.

[9] This definition includes the cases covered by **Rule A-21.6** [5] but is more general and applies even when indicated hydrogen is not necessary for distinguishing isomers. This definition has been adopted by the IUPAC Commission on Nomenclature of Organic Chemistry in "Revision of the extended Hantzsch-Widman System of Nomenclature of Heteromonocycles (Recommendations 1982)", **Rule RB-1.2**, *Pure Appl. Chem. 55* (1983) 409.

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N,N-Bis(trimethylsilyl)aminomethylation of Grignard Compounds— A Versatile Amine Synthesis

By *Hans Jürgen Bestmann** and *Gerhard Wölfel*

Dedicated to Professor Karl Winnacker on the occasion of his 80th birthday

Sodium bis(trimethylsilyl)amide **1**[1] reacts with primary halides **2** ($R^1=R'-CH_2$, R′=H, alkyl, alkenyl, alkynyl, aryl) to give *N,N*-bis(trimethylsilyl)amines **3**[2]. We have now converted the α-haloethers **4** with **1** into the *N,N*-bis(trimethylsilyl)aminomethyl ethers **5**. These react with the Grignard compounds **6** (R^1, see Table 1) to give the *N,N*-bis(trimethylsilyl)amines **7** and the magnesium alkoxides **8**. Table 1 shows the scope of the reaction. Grignard compounds **6** can be employed in which the MgBr residue is attached to an sp^3, sp^2 or sp hybridized C-atom. In the case of the propargyl moiety (Example **d** in Table 1), use of the aluminum "Grignard compound"[4] has once again[3] proven better than that of the magnesium compound.

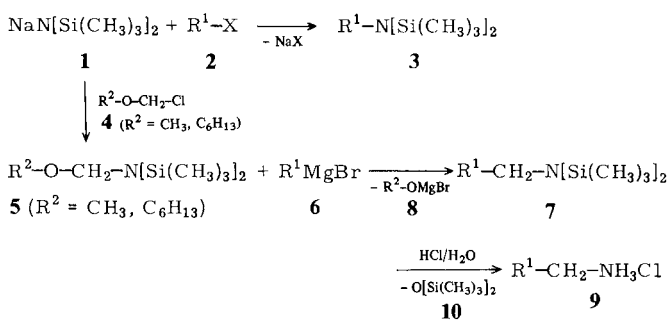

Table 1. Yields and boiling points of the *N,N*-bis(trimethylsilyl)amines **7**.

7	R^1	Yield [%] [a]	B.p. [°C/torr]
a	CH_3	82	60/20
b	$C_6H_5CH_2$	71 [b]	63/0.05
c	$H_2C=CH-CH_2$	70	81/16
d	$HC\equiv C-CH_2$ [c]	52	80/18
e	C_6H_5	64	52/0.1
f	α-Naphthyl	52	64/0.01
g	$H_7C_3-C\equiv C$	65	52/0.1

[a] Not optimized. [b] Same yields also in the reaction with **5b**. [c] The Al-"Grignard compound" was employed.

The silylamines **7** can easily be converted into the amine hydrochlorides **9** in yields of over 90% by treatment with 1 N hydrochloric acid or by passage of gaseous HCl into a solution of **7** in moist diethyl ether; the siloxane **10** is formed concomitantly[1].

Hence, primary halides such as **2** can either be converted into silylated amines such as **3** by nucleophilic substitution with **1** or, after umpolung via a Grignard compound, into compounds such as **7** containing an additional CH_2 group, by electrophilic substitution.

Procedure

5: **4** (0.1 mol) is added dropwise at 0°C to a stirred solution of **1** (18.4 g, 0.1 mol) in hexamethyldisilazane (50 mL). After 8 h at room temperature, NaCl is removed from the reaction mixture by filtration; the solvent is distilled off from the filtrate and the residue is fractionally distilled; **5a**; b.p. 73°C/16 torr; **5b**: b.p. 124°C/16 torr.—**7**: A solution of **5** (0.02 mol) in anhydrous ether (25 mL) is added dropwise to an ethereal Grignard solution of **2** (0.025 mol). After 12 h, precipitated **8** is filtered off and the solvent is removed from the filtrate by distillation. The residue is fractionally distilled. All operations are carried out under nitrogen.—**9**: HCl is passed into a solution of **7** (0.02 mol) in moist ether (25 mL). **9** precipitates out and is recovered by filtration.

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CAS Registry numbers:
1, 1070-89-9; **4a**, 107-30-2; **4b**, 39979-92-5; **5a**, 88211-44-3; **5b**, 88211-45-4; **6a**, 75-16-1; **6b**, 1589-82-8; **6c**, 1730-25-2; **6d**, 13254-27-8; **6e**, 100-58-3; **6f**, 703-55-9; **6g**, 41246-05-3; **7a**, 2477-39-6; **7b**, 58367-45-6; **7c**, 88211-46-5; **7d**, 88211-47-6; **7e**, 18406-59-2; **7f**, 88211-48-7; **7g**, 88211-49-8; **9a**, 557-66-4; **9b**, 156-28-5; **9c**, 17875-18-2; **9d**, 88211-50-6; **9e**, 3287-99-8; **9f**, 39110-74-2; **9g**, 88211-51-2.

[1] U. Wannagat, H. Niederprüm, *Chem. Ber. 94* (1961) 1540.
[2] K. Rühlmann, *Chem. Ber. 94* (1961) 2311; H. J. Bestmann, G. Wölfel, W. Rieck, *ibid.*, in press.
[3] Cf. H. J. Bestmann, R. Schobert, *Angew. Chem. 95* (1983) 810; *Angew. Chem. Int. Ed. Engl. 22* (1983) 780.
[4] E. Truscheit, K. Eiter, *Justus Liebigs Ann. Chem. 658* (1962) 65.

Stable Cyclopentadienylium Salts**

By *Rudolf Gompper** and *Heinrich Glöckner*

According to *Breslow*[1], cyclopentadienylium salts are antiaromatic compounds. The parent compound and the pentachloro derivative have a triplet ground state (cf. [2]), and the pentaphenyl and pentakis(*p*-methoxyphenyl) derivatives a low-lying triplet state.

Previously, cyclopentadienylium salts have only been obtained in solution. However, cyclopentadienylium ions can be dramatically stabilized by ring N atoms in a compound with donor substituents: azacyclopentadienylium salts[3] and 1,3-diazacyclopentadienylium salts are extraordinarily thermally stable and display no indication of antiaromaticity. Since the pentakis(*p*-methoxyphenyl)cyclopentadienylium ion is stable in solution at room temperature[5], it should be possible to find combinations of substituents which lead to isolable cyclopentadienylium salts;

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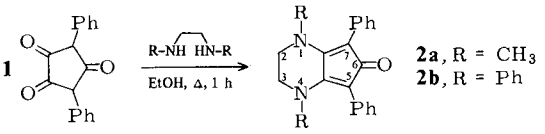
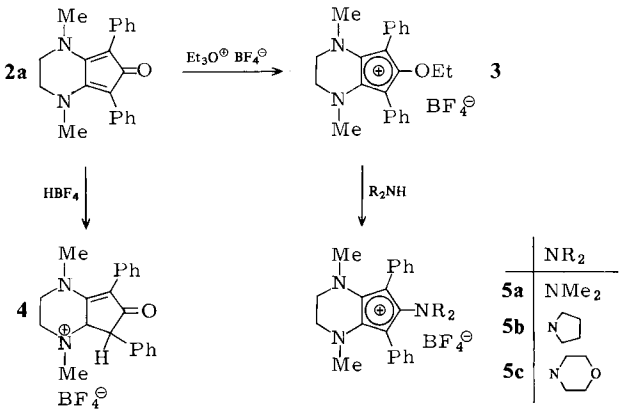
here, we report a route to stable cyclopentadienylium salts.



The diphenylcyclopentanetrione **1** condenses smoothly with *N,N'*-dimethyl- and *N,N'*-diphenylethylenediamine to afford the red cyclopentadienone derivative **2**[7] (for the reaction of **1** with *o*-phenylenediamine, cf. [6]).

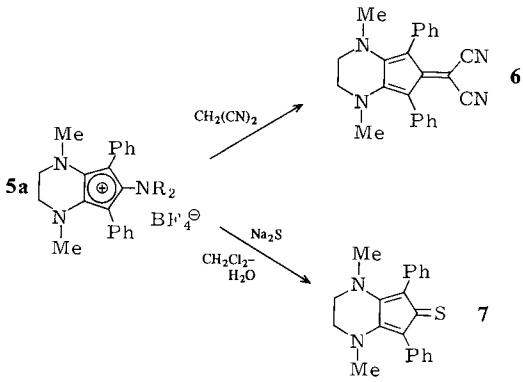
The relatively low CO stretching frequency of **2** suggests that the two amino groups of the piperazine ring are strongly conjugated with the carbonyl group and with an *O*-nucleophile, comparable to simple β-aminovinylcarbonyl compounds.



Protonation of **2a** with tetrafluoroboric acid affords the yellow salt **4** [100%, m.p. = 197 °C (decomp.); IR (KBr): ν = 1707, 1673, 1618, 1600, 1084 cm^{-1}], i.e. instead of the expected *O*-protonation, *C*-protonation occurs. In contrast, only *O*-alkylation occurs in the reaction of **2a** with triethyloxonium tetrafluoroborate (1.2 equiv. freshly prepared $Et_3O^{\oplus}BF_4^{\ominus}$, CH_2Cl_2, 25 °C, 1 h), resulting in formation of the ethoxycyclopentadienylium salt **3** in practically quantitative yield[7] as a green oil which occasionally solidifies amorphously.

3 is stable up to ca. 40 °C, but is very sensitive to moisture. More thermally stable cyclopentadienylium salts are accessible by allowing **3** to react with secondary amines (the reaction solution containing **3** is treated successively with 3 equivalents of amine and water, the dichlormethane separated off, and the mixture dried and covered with a layer of ether). The blue 6-amino-1,4-dimethyl-5,7-diphenyl-1,2,3,4-tetrahydrocyclopentapyrazin-6-ylium tetrafluoroborates **5** result[7]. The synthesis of crystalline, stable cyclopentadienylium salts **5** goes a long way towards stable cyclopentadienylium salts with a triplet ground state. The UV/VIS spectra of **3** and **5** indicate that the longest wavelength absorption maximum corresponding to the calculated (HMO) reduction in the HOMO-LUMO separation is bathocronically shifted (620, 624, 635, 735 nm) as the donor strength of the substituent at the 6-position decreases. Combinations of substituents which allow a triplet ground state should therefore also exist within the framework of the model compounds **3** and **5**.

3 and **5** can be used as starting materials for the synthesis of further cyclopentadiene derivatives. For example, from **5** and sodium sulfide in CH_2Cl_2/H_2O the cyclopentadienethione **7** is obtained [78%, m.p. = 195 °C (decomp.), blue, lustrous lamellae; UV/VIS (CH_3CN):



$\lambda_{max}(\lg\varepsilon)$ = 305 (4.13), 388 (4.49), 645 nm (2.72)]; **7** is the first stable cyclopentadienethione. Using malononitrile (NaH, tetrahydrofuran, Δ, 10 min) the donor-acceptor substituted fulvene **6** is accessible [80%, m.p. = 230 °C (decomp.), blue, lustrous lamellae; UV/VIS ($CHCl_3$): $\lambda_{max}(\lg\varepsilon)$ = 391 (4.58), 4.05 (sh), 510 (sh), 602 nm (2.86)].

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CAS Registry numbers:
1, 7003-69-2; **2a**, 88288-78-2; **2b**, 88288-79-3; **3**, 88288-81-7; **4**, 88288-83-9; **5a**, 88288-85-1; **5b**, 88288-87-3; **5c**, 88288-89-5; **6**, 88288-90-8; **7**, 88288-91-9; $CH_2(CN)_2$, 109-77-3; *N,N'*-dimethylethylenediamine, 110-70-3; *N,N'*-diphenylethylenediamine, 150-61-8

[1] R. Breslow, *Acc. Chem. Res. 6* (1973) 393.
[2] R. Breslow, *Pure Appl. Chem. 54* (1982) 927.
[3] R. Gompper, M. Junius, *Tetrahedron Lett.* **21** (1980) 2883.
[4] R. Gompper, K. Bichlmayer, *Angew. Chem. 91* (1979) 170; *Angew. Chem. Int. Ed. Engl. 18* (1979) 156.
[5] W. Broser, H. Kurreck, P. Siegle, *Chem. Ber. 100* (1967) 788.
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[7] **2a**: yield 83%, m.p. = 219–222 °C, red-violet needles (from ethanol), UV/VIS (CH_3CN): $\lambda_{max}(\lg\varepsilon)$ = 305 (4.49), 510 nm (2.51); IR (KBr): ν = 1667, 1611, 1595 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ = 2.77 (s; 6H, NCH_3), 3.24 (s; 4H, NCH_2CH_2N), 7.16 (s; 10H, arene-H); ^{13}C-NMR ($CDCl_3$): δ = 41.90 (q; CH_3), 49.80 (quint; C-2/3), 98.59 (s; C-5/7), 125.21 (d; C-*p*), 127.12, 130.97 (d; C-*o/m*), 133.76 (s; C-*i*), 150.87 (s; C-4a/7a), 195.00 (s; C-6).— **2b**: 61%, decomp. >320 °C, sparingly soluble red-violet powder; IR (KBr): ν = 1660, 1632, 1607 cm^{-1}.— **3**: UV/VIS (Ac_2O): λ_{max} = 292, 420, 735 nm; ^{1}H-NMR ($CDCl_3$): δ = 1.03 (t; 3H, OCH_2CH_3), 2.79 (s; 6H, NCH_3), 3.70 (q; 2H, OCH_2CH_3), 3.67 (s; 4H, NCH_2CH_2N), 7.23 (s; 10H, arene-H).— **5a**: 87%, m.p. = 146 °C (decomp.), blue needles (from *i*PrOH); UV/VIS (CH_2Cl_2): $\lambda_{max}(\lg\varepsilon)$ = 286 (4.01), 353 (3.40), 438 (sh), 624 nm (2.71); IR (KBr): ν = 1622, 1597, 1565, 1053 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ = 2.64 (s; 12H, NCH_3), 3.48 (s; 4H, NCH_2CH_2N), 7.24 (s; 10H, arene-H); ^{13}C-NMR ($CDCl_3$): δ = 41.62 (q; NCH_3), 45.59 (q; $N(CH_3)_2$), 49.77 (t; C-2/3), 95.90 (s; C-5/7), 128.10 (d; C-*p*), 128.73, 132.61 (d; C-*o/m*), 134.54 (s; C-*i*), 150.93 (s; C-4a/7a), 176.83 (s; C-6).— **5b**: blue needles (from *i*PrOH), m.p. = 181 °C (decomp.).— **5c**: 95%, green-blue needles (from CH_2Cl_2/Et_2O), m.p. = 125 °C (decomp.).

Hydroxide Ion-Initiated Deuteration of Very Weak CH Acids under Phase Transfer Catalysis Conditions**

By *Marc Halpern, David Feldman, Yoel Sasson,* and *Mordecai Rabinovitz**

Use of aqueous sodium hydroxide under phase transfer catalysis conditions (PTC/$OH^{\ominus}$ systems) has been ac-

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[**] Hydroxide Ion-Initiated Reactions under Phase Transfer Conditions, Part 7. This work is taken in part from the Ph. D. Thesis of *M. Halpern* and the M. Sc. Thesis of *D. Feldman*.— Part 6: *J. Org. Chem. 50* (1984), in press.

cepted as the method of choice for many base catalyzed organic reactions. Thus CH acids have been deuterated in the presence of quaternary ammonium salts[1–4]. Deuteration has, however, been limited to compounds as or more acidic than thiazole[3]. Recently, we showed that the hydroxide ion may be extracted into the organic phase under PTC/$OH^{\ominus}$ conditions[5]. Because of the differences in their relative states of hydration, the basicity of the extracted hydroxide ion is expected to be greater than that of hydroxide ion at the interface. This enhanced basicity may be used to significantly extent the scope of PTC/$OH^{\ominus}$ base catalyzed reactions. Here, we report the deuteration of very weak CH acids (up to pK_a 34)[6e] under extractive PTC/$OH^{\ominus}$ conditions.

When 550 mg (3.27 mmol) of diphenylmethane ($pK_a = 33$)[6a] is stirred magnetically at 27 °C for 16 h in a closed vessel in the presence of 1.5 mL of 18.3 M NaOD/D_2O and 200 mg (0.59 mmol) of tetrabutylammonium hydrogen sulfate (TBA HSO_4), 540 mg of α,α′-dideuteriodiphenylmethane (97%) is obtained after work-up (dilution in dichloromethane/water, washing with water, drying, and evaporation). The methylene singlet at $\delta = 3.72$ totally disappears in the NMR spectrum. The mass spectrum of the isolated compound shows the molecular ion at *m/z* 170.

Allylbenzene ($pK_a = 34$)[6b] was quantitatively isomerized and simultaneously deuterated at 75 °C yielding *trans*- and *cis*-PhCH=$CHCH_2D$. This indicates that isomerization is more rapid than deuterium exchange at the α-position, and that β-methylstyrene is not acidic enough to react further. The product was identified by ^{1}H-NMR spectroscopy and by the characteristic C-D splitting pattern (3 peaks of equal height, $J = 20$ Hz) in the ^{13}C-NMR spectrum. Under the same conditions, toluene ($pK_a = 41$)[6a] does not undergo deuteration. Taking into account the fact that allylbenzene reacts in the given systems, but β-methylstyrene and toluene do not, it may be concluded that the limit of the basicity of the hydroxide ion under these conditions is in the range $pK_a \approx 34-41$.

10,11-Dibenzo[*a*,*d*]cycloheptadiene ($pK_a = 31$)[6a] and xanthene ($pK_a = 27$)[6c] were quantitatively dideuterated at the acidic position after 20 h and 3 h, respectively, in the presence of 10 mol% TBA HSO_4 and 63% NaOD/D_2O (solid material). Under similar conditions the aromatic hydrogens of 1,2,3,4-tetrafluorobenzene ($pK_a = 31.5$[6d] were exchanged to at least 80% for deuterium (^{1}H-NMR CI-MS).

An attempt to deuterate triphenylmethane ($pK_a = 31.5$)[6a] in chlorobenzene surprisingly afforded only 25% deuterium exchange with 10 mol% TBA HSO_4 after 24 h and 70% deuterium exchange with 20 mol% methyltrioctylammonium hydrogen sulfate at 75 °C, the reaction terminating after 2 h due to decomposition of the catalyst. In the presence of tetraoctylammonium bromide no reaction was observed, since $Br^{\ominus}$ apparently suppresses $OH^{\ominus}$ extraction sufficiently to prevent significant deprotonation of the sterically hindered substrate. Chlorobenzene was found to be a suitable solvent for the deuteration of diphenylmethane.

Thus, we believe that it is worthwhile to consider the use of a nonaccessible quaternary ammonium salt paired with a hydrophilic counterion (*e.g.*, NR_4HSO_4) as the catalyst in PTC/$OH^{\ominus}$ reactions requiring strong basic activity.

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[2] I. Willner, M. Halpern, M. Rabinovitz, *J. Chem. Soc. Chem. Commun. 1978*, 155.
[3] W. Spillane, P. Kavanagh, F. Young, H. J.-M. Dou, J. Metzger, *J. Chem. Soc. Perkin Trans. I 1981*, 1763.
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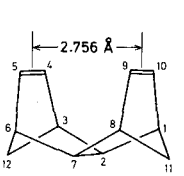
[6] a) A. Streitwieser, J. Murdoch, G. Hafelinger, C. Chang, *J. Am. Chem. Soc. 95* (1973) 4248; b) K. Bowden, R. Cook, *J. Chem. Soc. Perkin Trans. II* (1972) 1407; c) D. J. Cram, *Fundamentals of Carbanion Chemistry*, Academic Press, New York 1965; d) A. Streitwieser, P. Scannon, H. Niemeyer, *J. Am. Chem. Soc. 94* (1972) 7936; e) It should be noted that pK_a values are strongly influenced by the solvent and the base: W. S. Matthews, J. E. Bares, J. E. Bartness, F. G. Bordwell, F. J. Cornforth, G. E. Drucker, Z. Margolin, R. J. McCallum, G. J. McCallum, N. R. Vanier, *J. Am. Chem. Soc. 97* (1975) 7006.

Structure of Tetracyclo[6.2.1.1^{3,6}.0^{2,7}]dodeca-4,9-diene: A Diolefin with Close Double Bonds**

By *Otto Ermer**, *Claus-Dieter Bödecker*, and *Hans Preut*

Calculations with our consistent force field gave a C_{2v} symmetric structure for tetracyclo[6.2.1.1^{3,6}.0^{2,7}]dodeca-4,9-diene **1** in which the double bonds are only 2.756 Å apart and have almost parallel planes[1]. Here, we report the crystal structure analysis of the derivative **2**, which we performed to examine the computational results (Fig. 1)[2].



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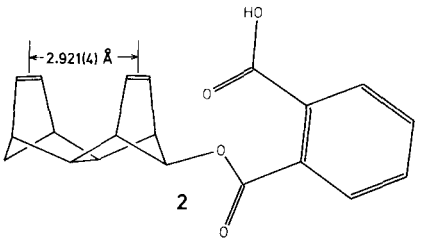

2

In the crystals of **2**, the tetracyclic carbon framework has, to a good approximation, C_{2v} symmetry. The measured distance between the olefinic double bonds is 2.921(4) Å (corrected for libration 2.933 Å) and thus exceeds the calculated value by 0.165 (corr. 0.177) Å. Correspondingly, the observed (C_{2v} averaged) angle C(1)-C(2)-C(3) is larger than that calculated (125.4(0.3) vs. 121.3°).

The discrepancies between the calculated and observed geometries therefore indicate that the close double bonds in **1** repel each other more strongly than predicted by our force field. The obvious conclusion that the C···C nonbonding potential in our force field is not repulsive enough at short distances, however, *cannot be drawn in general* from the present study. In fact, the larger observed distance between the double bonds in **1** is rather a consequence of orbital symmetry effects as expressed in the rules of *Woodward* and *Hoffmann*[3]. The approach of two parallel double bonds as in **1** is part of a process which in the electronic ground state is energetically particularly unfavorable (symmetry-forbidden) and thus associated with

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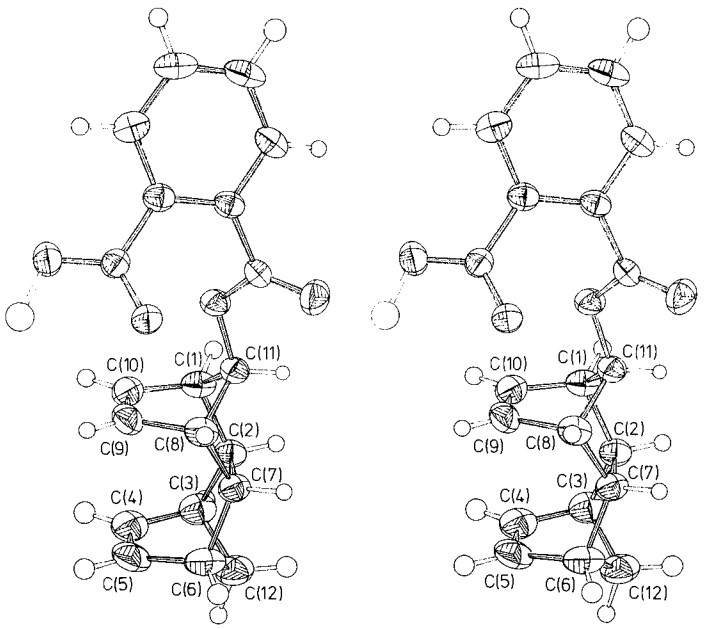
extra non-bonding repulsions. Effects of this nature are not represented in our force field since no data of olefins with close double bonds were available at the time of its calibration. It is noted that *Allinger*'s MM2 force field[4] also gives a smaller distance (2.787 Å) between the double bonds in **1** than that observed for **2**.



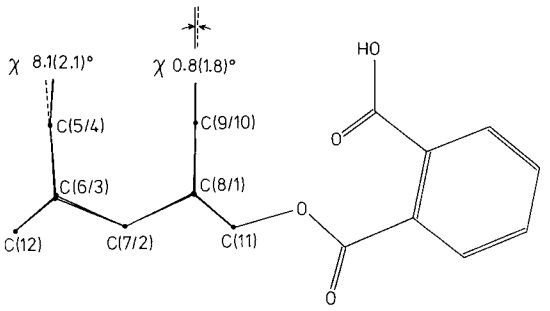


Fig. 1. Crystal structure of **2**. Top: Stereoscopic view with vibrational ellipsoids (35%) for the heavy atoms; for clarity, the isotropic temperature factors of the H atoms are reduced by a common factor. Below: Newman projection along C(7)-C(2).

It is to be expected that in **1** the repulsion between the double bonds is also alleviated by a shift of π electron density from the *endo*- to the *exo*-sides of the norbornene moieties, which is larger than in norbornene[5] itself. The structural consequence should be particularly large pyramidalizations—larger than those calculated for **1** or norbornene with our force field—at the C(sp^2) atoms (symmetric out-of-plane bending) with the H atoms of the double bonds approaching each other. In the crystals of **2**, the double bond C(4)=C(5) is indeed relatively strongly bent inwards by $\chi = 8.1(2.1)°$ (Fig. 1, below); using our force field we calculate only 3.1°[1] for **1** and 4.5° for norbornene. Interestingly, in **2** the double bond C(9)=C(10) is only slightly bent inwards ($\chi = 0.8(1.8)°$). This might be due to the substitution by the electronegative oxygen atom at C(11), which counteracts an accumulation of π electron density on the *exo*-side of the C(9)=C(10) double bond. Quantum chemical calculations on analogous C(7)-substituted norbornenes produced a similar effect[5]. Obviously, these interpretations have to be backed by a more reliable experimental localization of the H atoms in **2** than is possible by X-ray methods.

Our crystallographic results lead to the remarkable conclusion that in the symmetry-forbidden, synchronous dimerization of ground-state ethylene (conservation of overall D_{2h} symmetry, parallel double bond planes) symmetric out-of-plane bending deformations with *inward* displacements of the H atoms occur initially. These displacements are reversed only on closer approach of the ethylene molecules until eventually cyclobutane is formed (Fig. 2). A good quantum mechanical calculation would be of interest to verify this prediction quantitatively. The tetracyclododecadiene **1** with its almost parallel double bonds enforced by the ring fusion, therefore, represents a model for a "frozen" educt geometry in the initial stage of the symmetry-forbidden formation of cyclobutane from two molecules of ethylene.

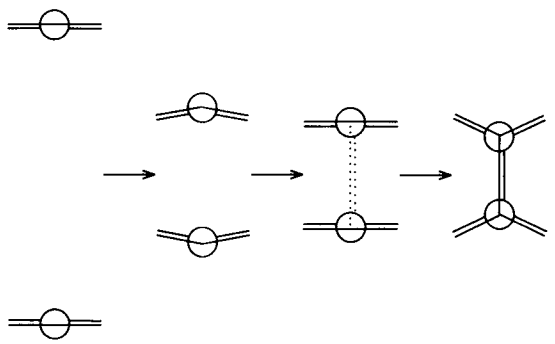


Fig. 2. Proposed qualitative geometry changes (Newman projections) in the course of the symmetry-forbidden dimerization of ethylene (Electronic ground state, overall D_{2h} symmetry).

The computationally underestimated repulsion between the double bonds in **1**, and thus the likewise underestimated total strain, manifests itself also in properties other than structure. Thus the heat of hydrogenation calculated for **1** with our force field (-27.90 kcal mol^{-1} including vibrational corrections[1], hydrogenation of one double bond) has a magnitude more than 6 kcal mol^{-1} lower than the measured value (-34.15 kcal mol^{-1}[6a]). A further indication of the substantial destabilizing interaction between the double bonds comes from the PE spectroscopic finding that **1** is 0.52 eV more readily ionizable than the monoolefin tetracyclo[6.2.1.1^{3,6}.0^{2,7}]dodec-4-ene[6h]. Finally, for similar reasons, in the dibenzo compound of **1** smaller distances between the benzene rings are calculated by force field methods[1] than observed crystallographically[6c].

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CAS Registry number:
2, 88295-40-3.

[1] O. Ermer: *Aspekte von Kraftfeldrechnungen*, Wolfgang Baur Verlag, München 1981.

[2] Monoclinic crystals (from acetone); m.p. = 157°C; space group $P2_1/n$, $Z = 4$, $a = 9.985(2)$, $b = 12.394(2)$, $c = 13.618(2)$ Å, $\beta = 108.49(2)°$; intensity measurements at room temperature on a four-circle diffractometer; structure solution by direct methods; refinement using 2406 reflections with $|F_0| > 0$; $R = 0.069$, $R_w = 0.065$ (0.052 and 0.058, respectively, using 1905 reflections with $|F_0| > 3\sigma(F_0)$); all crystallographic calculations with the SHELX 76 program. Further details of the crystal structure investigation can be obtained from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen by quoting the depository number CSD 50606, the names of the authors, and the journal citation.

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[3] R. B. Woodward, R. Hoffmann, *Angew. Chem. 81* (1969) 797; *Angew. Chem. Int. Ed. Engl. 8* (1969) 781.
[4] N. L. Allinger, *J. Am. Chem. Soc. 99* (1977) 8127.
[5] See: N. G. Rondan, M. N. Paddon-Row, P. Caramella, K. N. Houk, *J. Am. Chem. Soc. 103* (1981) 2436.
[6] a) R. B. Turner, A. D. Jarrett, P. Goebel, B. J. Mallon, *J. Am. Chem. Soc. 95* (1973) 790. b) H.-D. Martin, B. Mayer, *Angew. Chem. 95* (1983) 281; *Angew. Chem. Int. Ed. Engl. 22* (1983) 283. c) H. Prinzbach, G. Sedelmeier, C. Krüger, R. Goddard, H.-D. Martin, R. Gleiter, *ibid. 90* (1978) 297; *17* (1978) 271.

Radical Anion-Substituted Crown Ethers as Cages for Metal Cations**

By *Hans Bock**, *Bernhard Hierholzer*, *Fritz Vögtle*, and *Günter Hollmann*

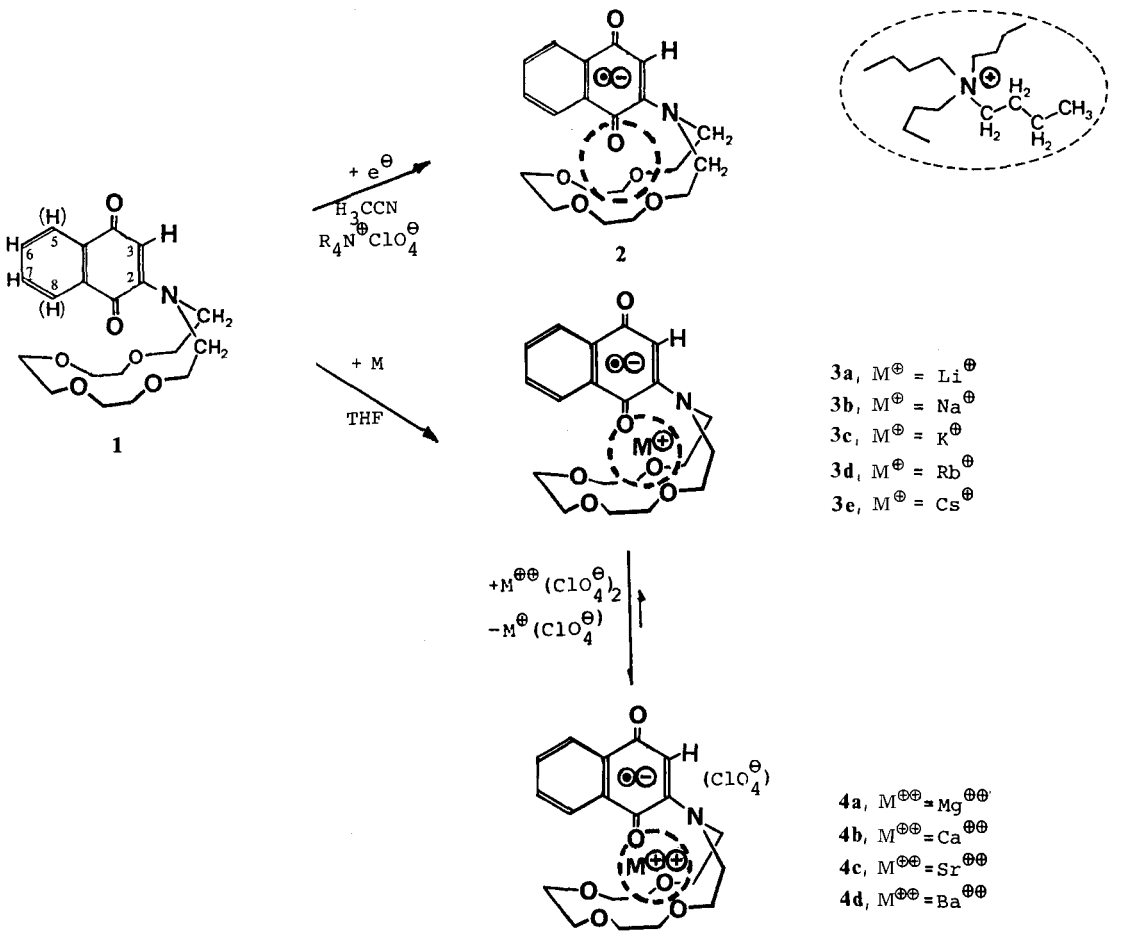
Dedicated to Professor Karl Winnacker on the occasion of his 80th birthday

Exploring membrane transport phenomena, *Frensdorff* and *Pedersen* as well as *Lehn* have demonstrated in classical studies that macrocyclic polyethers selectively form metal cation complexes[1]. Among the various facets of the expansive research area, ion-selective crown ether dyes[2] will be emphasized here; these allow the interactions between metal cations and a structurally fixed solvate cage to be investigated. As a sensitive measurement probe for ion-pair radicals, ESR/ENDOR spectroscopy has been recommended[3]; in the following we report for the first time on the spin distribution in radical anion-substituted crown ethers and its dependence on the charge and radius of the complexed metal cation.

If 1,4-naphthoquinone **1**, substituted in the 2-position with tetraoxomonoaza[15]crown-5, is electrochemically reduced in an acetonitrile solution containing tetra(*n*-butyl)ammonium perchlorate, the azacoronand-naphthoquinone radical anion is generated. This exhibits a vacant solvate cage, for which the counterion tetra(*n*-butyl)ammonium proves to be too bulky.

If, on the other hand, the reduction is carried out using alkali metals in tetrahydrofuran (THF) at room temperature, ion-pair radicals **3** form whose ENDOR spectra (cf. Fig. 1 for $M^{\oplus}=K^{\oplus}$) show the six line-pairs expected for six different types of protons.

The fixation of the metal cation in the solvate cage of the azacoronand-naphthaquinone radical anion is suggested by the following observations:



- On addition of an excess of [2.2.2]cryptand, which complexes $K^{\oplus}$ more strongly[1b], an ESR spectrum results which is identical with that of the electrochemically generated radical anion.
- In the ENDOR spectra of the complexes couplings with metal ions are detected; the coupling constants are, e.g. $a_{Li^{\oplus}}=0.028$ mT for lithium or $a_{Cs^{\oplus}}=0.174$ mT for cesium.

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[**] Radical Ions, Part 59.—Part 58: H. Bock, B. Hierholzer, H. Kurrek, W. Lubitz, *Angew. Chem. 95* (1983) 817; *Angew. Chem. Int. Ed. Engl. 22* (1983) 787; *Angew. Chem. Suppl. 1983*, 1088. Cf. also G. Hollmann, F. Vögtle, *Chem. Ber.*, in press.

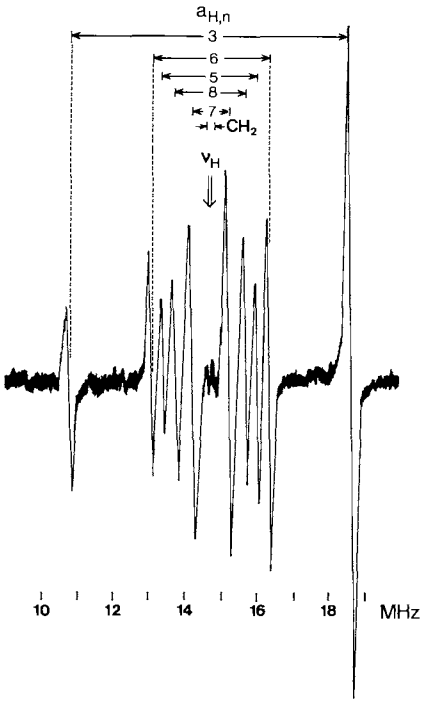

Fig. 1. ^{1}H-ENDOR-spectrum of **3c** at 202 K. Measurement conditions: 9–20 MHz, microwave power 9 dB, radiowave power 150 W, duration of recording 2000 s, time constant 1 s. Assignment according to INDO open-shell calculation for 2-dimethylaminonaphthoquinone radical anion ($a_{H,3} > a_{H,6} > a_{H,5} \approx a_{H,8} > a_{H,7} > a_{HNCH_3}$).

- The ESR spectra of the ion-pairs **3** reported here do not show the temperature-dependence known for quinone radical anions[4]. No ^{14}N-coupling can be observed, a finding, which is consistent with a fixation of the *N*-electron pair in the naphthaquinone π-nodal plane and directed outwards from the solvate cage, and thus with a rigidization of the molecular skeletal framework on metal-cation complexation.
- Addition of anhydrous alkaline-earth perchlorates in THF leads to a significant change in the ESR data, as expected for an increased charge of the complexed cations **4**.

In the ESR/ENDOR spectra of the radical anions of the naphthoquinone-crownether-metal complexes presented here (cf. Fig. 1), the largest coupling, assigned to the proton in position 3, reveals most markedly its dependence on charge and radius of the metal cation (Fig. 2), as is typical for contact ion-pair interactions[3].

The measurement data (Fig. 2), can be rationalized straightforwardly by an increase of the spin population at

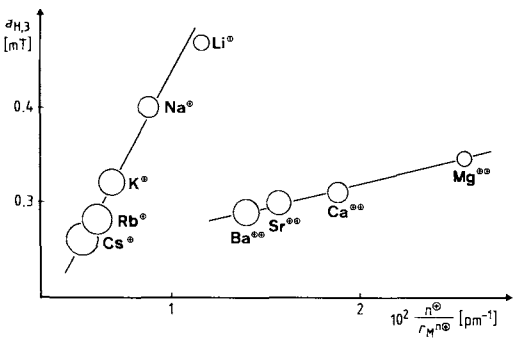

Fig. 2. Correlation of the coupling constants $a_{H,3}$ of the radical anions **3** and **4** with charge $n^\oplus$ and radius $1/r_{M^{n\oplus}}$ of the complexed metal ions.

the center 3 of the naphthoquinone radical anion, caused by the $M^{n\oplus}$-induced electron density flux to the quinone oxygen of the contact ion-pair [π-C→O$^\ominus \cdots M^{n\oplus}$].

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1, 77101-98-5; **2**, 88288-46-4; **3a**, 88288-47-5; **3b**, 88288-48-6; **3c**, 88288-49-7; **3d**, 88288-50-0; **3e**, 88288-51-1; **4a**, 88288-53-3; **4b**, 88288-55-5; **4c**, 88295-44-7; **4d**, 88288-57-7.

[1] a) C. J. Pedersen, H. K. Frensdorff, *Angew. Chem. 84* (1972) 16; *Angew. Chem. Int. Ed. Engl. 11* (1972) 16. b) J. M. Lehn, *Acc. Chem. Res. 11* (1978) 49; c) cf. the summaries by F. Vögtle, E. Weber, U. Elben in *Kontakte 1981* No. 1 p. 24 and references cited therein.
[2] J. P. Dix, F. Vögtle, *Angew. Chem. 90* (1978) 893; *Angew. Chem. Int. Ed. Engl. 17* (1978) 857; *Chem. Ber. 114* (1981) 638.
[3] Cf. M. Lubitz, M. Plato, K. Möbius, R. Biehl, *J. Phys. Chem. 83* (1979) 3402, and references cited therein.
[4] Cf. *e.g.* M. Brustolon, L. Pasimeni, C. Corvaja, *J. Chem. Soc. Faraday Trans. 2 71* (1975) 193; R. Allendoerfer, D. Eustall, *J. Phys. Chem. 75* (1971) 2765.

Heterometal Binuclear Complexes with Thio- and Selenoformaldehyde as Bridge Ligands**

By *Helmut Werner** and *Wilfried Paul*

Recently, three independent research groups reported the successful fixation of CH_2Se, a molecule which is extremely unstable in the free state, by complexation in transition-metal complexes[1]. *Headford* and *Roper*[1a], like us[1c], used an iodo(iodomethyl)metal compound $L_nM(CH_2I)I$ as starting material and converted this by reaction with NaSeH into the corresponding selenoformaldehyde complex $L_nM(\eta^2\text{-}CH_2Se)$, in which ($L_nM = (PPh_3)_2(CO)_2Os$[1a], $C_5H_5(PMe_3)Rh$[1c]). *Herrmann* et al.[1b] chose another synthetic concept, namely that of methylene addition to bonds between main group elements and transition metals, and thus obtained from (μ-Se)[$Mn(CO)_2C_5R_5$]$_2$ (R = H, Me) and diazomethane the binuclear complex (μ-CH_2Se)[$Mn(CO)_2C_5R_5$]$_2$; in these dimanganese compounds two *identical* metal-complex fragments are bridged by the CH_2Se ligand.

Structurally similar compounds, but with two *different* metal-ligand groups bridged by CH_2Se, are readily obtainable from the mononuclear rhodium complex **1** and the tetrahydrofuran adducts $M(CO)_5 \cdot THF$ (M = Cr, W) or $C_5H_5Mn(CO)_2 \cdot THF$[2]. The structure proposed for the products **2-4** is in good agreement with the spectroscopic data summarized in Table 1. In the ^{1}H-NMR spectra, the occurrence of two signals for the diastereotopic CH_2Se protons is characteristic; they are shifted upfield compared to the signals of **1**[1c]. The difference in the δ-values of the CH_2 signals is substantially greater than in the case of the dimanganese compounds (μ-CH_2Se)[$Mn(CO)_2C_5R_5$]$_2$, in which it is 0.22 (R = H) and 0.70 ppm (R = Me)[1b].

The sulfur atom of a mononuclear (η^2-CH_2S)-metal compound can also function as donor towards a 16-electron complex fragment such as $Cr(CO)_5$: Compound **6** is

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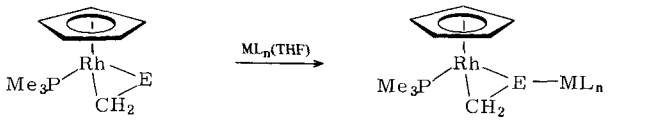
Table 1. Spectroscopic data of the complexes **2**-**4** and **6**.

	2		**3**		**4**		**6**	
IR:								
ν(CO) [cm^{-1}]	2050, 1980 1930, 1900 (in THF)		1985, 1930 1925, 1910 (in pentane)		1960, 1900 1830 (in Nujol)		1975, 1935 1930, 1920 (in pentane)	
^{1}H-NMR [a]:								
$\delta(C_5H_5Rh)$	5.13 (dd)		5.17 (dd)		5.41 (dd) [b]		5.07 (dd)	
J(RhH)	0.7		0.7		0.6		0.7	
J(PH)	1.2		1.2		1.4		1.1	
$\delta(CH_2)$ (2 × 1 H)	4.88 (dd),	3.56 (ddd)	5.18 (ddd),	3.76 (ddd)	4.72 (dd),	3.54 (ddd)	3.97 (dd),	2.67 (ddd)
J(RhH)	2.0	1.0	2.0	0.8	2.2	0.8	0.6	0.4
J(PH)		10.6	0.7	10.5		10.2		7.8
J(HH)	1.0	1.0	0.8	0.8	0.8	0.8	1.5	1.5
$\delta(Me_3P)$	0.66 (dd)		0.71 (dd)		1.32 (dd)		0.57 (dd)	
J(RhH)	1.0		1.0		1.0		0.8	
J(PH)	10.2		10.4		10.3		10.2	
^{31}P-NMR (in C_6D_6):								
δ	2.29 (d)		2.31 (d)		2.39 (d)		2.37 (d)	
J(RhH)	166.7		168.2		174.2		169.7	

[a] **2**, **3**, and **6** in C_6D_6, **4** in [D$_6$]acetone. [b] $\delta(C_5H_5Mn) = 4.38$ (s).

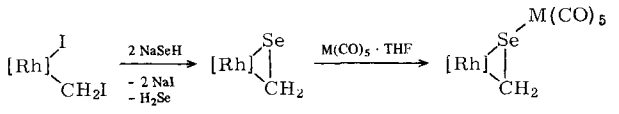


1, E = Se; **5**, E = S

2, E = Se, ML_n = $Cr(CO)_5$
3, E = Se, ML_n = $W(CO)_5$
4, E = Se, ML_n = $Mn(CO)_2C_5H_5$
6, E = S, ML_n = $Cr(CO)_5$

formed from **5**[1c] and $Cr(CO)_5 \cdot THF$ under the same conditions as for the reaction **1** → **2**[2]. A corresponding binuclear complex in which a thioformaldehyde ligand bridges two $Mn(CO)_2C_5H_5$ fragments was prepared by *Herberhold* et al. using Herrmann's route[3].

The possible general applicability of the method developed for the synthesis of **1** and **5** is demonstrated by the synthesis of **7**[4] from $C_5Me_5(CO)Rh(CH_2I)I$[5]. The selenoformaldehyde complex **7** also behaves like a Lewis base and reacts with $M(CO)_5 \cdot THF$ (M = Cr, Mo) to give the heterometal binuclear complexes **8** and **9**[4]. This indicates that neutral CH_2S- and CH_2Se-transition-metal compounds presumably react in general as two-electron donors, both towards alkylating agents[1a,c] as well as towards complex fragments such as $Cr(CO)_5$, $Mn(CO)_2C_5H_5$, etc. The cation $[C_5H_5Re(\eta^2\text{-}CH_2S)(NO)PPh_3]^{\oplus}$ does not appear to be capable of this[6], possibly due to the positive charge, and the consequently lower electron density at the sulfur atom.



7

[Rh] = $C_5Me_5(CO)Rh$

8, M = Cr; **9**, M = Mo

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1, 85202-36-4; **2**, 88288-37-3; **3**, 88288-38-4; **4**, 88288-39-5; **5**, 85202-35-3; **6**, 88288-40-8; **7**, 88288-41-9; **8**, 88288-42-0; **9**, 88288-43-1.

[1] a) C. E. L. Headford, W. R. Roper, *J. Organomet. Chem. 244* (1983) C 53; b) W. A. Herrmann, J. Weichmann, R. Serrano, K. Blechschmitt, H. Pfisterer, M. L. Ziegler, *Angew. Chem. 95* (1983) 331; *Angew. Chem. Int. Ed. Engl. 22* (1983) 314; *Angew. Chem. Suppl. 1983*, 363-395; c) W. Paul, H. Werner, *Angew. Chem. 95* (1983) 333; *Angew. Chem. Int. Ed. Engl. 22* (1983) 316; *Angew. Chem. Suppl. 1983*, 396–404.

[2] General procedure: A solution of $M(CO)_6$ or $C_5H_5Mn(CO)_3$ (1.0 mmol) in THF (50 mL) is irradiated until evolution of CO ceases (*ca.* 2–3 h). After addition of 100 mg (0.3 mmol) **1** [1c], the solution is stirred for ca. 24 h at room temperature, the solvent removed in vacuo, and the residue extracted with benzene. The extract is concentrated to a few mL and chromatographed on Al_2O_3 (Woelm, Activity IV) with benzene. Recrystallization of the products from pentane; yield 59% (**2**), 28% (**3**) and 87% (**4**), respectively. The preparation of **6** from $Cr(CO)_6$ and **5** is carried out analogously; yield 20%.—**2**: orange crystals, m.p. 128°C (dec.), relative molecular mass M_r = 530 (MS); ^{13}C-NMR [400 MHz, 25°C, C_6D_6, int. TMS]: δ(CO-*trans*) = 222.83 (s), δ(CO-*cis*) = 218.50 (s), $\delta(C_5H_5)$ = 87.64 (s), $\delta(CH_2)$ = 43.06 (dd, J_{RhC} = 22.3, J_{PC} = 7.9 Hz), $\delta(Me_3P)$ = 17.94 (d, J_{PC} = 32.5 Hz).—**3**: orange crystals, m.p. 31°C (dec.), M_r = 662 (MS).—**4**: dark red crystals, m.p. 117°C (dec.), M_r = 514 (MS).—**6**: yellow crystals, m.p. 96°C (dec.), M_r = 482 (MS).

[3] M. Herberhold, W. Ehrenreich, W. Bühlmeyer, *Angew. Chem. 95* (1983) 332; *Angew. Chem. Int. Ed. Engl. 22* (1983) 315.

[4] **7** can be prepared analogously to **1** [1c] from $C_5Me_5(CO)Rh(CH_2I)I$ [5] and NaSeH; yield 73%. The synthesis of **8** and **9** proceeds analogously to that of **2**–**4**; yield 39 and 88%, respectively.—**7**: red crystals, m.p. 119°C (decomp.), M_r = 360 (MS); IR [Nujol]: ν(CO) = 2010 cm^{-1}; ^{1}H-NMR [C_6D_6]: $\delta(C_5Me_5)$ = 1.69 (d, J_{RhH} = 0.4 Hz), $\delta(CH_2)$ = 5.56 (dd, J_{RhH} = 0.7, J_{HH} = 2.0 Hz) and 4.56 (dd, J_{RhH} = 2.0, J_{HH} = 2.0 Hz).—**8**: dark red crystals, m.p. 85°C (dec.), M_r = 552 (MS); IR [pentane]: ν(CO) = 2058, 2020, 1940, 1935, 1925 cm^{-1}; ^{1}H-NMR [C_6D_6]: $\delta(C_5Me_5)$ = 1.35 (d, J_{RhH} = 0.5 Hz), $\delta(CH_2)$ = 4.93 (dd, J_{RhH} = 0.2, J_{HH} = 0.7 Hz) and 3.88 (dd, J_{RhH} = 2.5, J_{HH} = 0.7 Hz).—**9**: red crystals, m.p. 84°C (dec.), M_r = 598 (MS); IR [pentane]: ν(CO) = 2065, 2055, 2020, 1990, 1940, 1925 cm^{-1}; ^{1}H-NMR [C_6D_6]: $\delta(C_5Me_5)$ = 1.49 (d, J_{RhH} = 0.5 Hz), $\delta(CH_2)$ = 5.09 (dd, J_{RhH} = 0.2, J_{HH} = 4.9 Hz) und 4.09 (dd, J_{RhH} = 2.3, J_{HH} = 4.9 Hz).

[5] H. Werner, W. Paul, *J. Organomet. Chem. 236* (1982) C 71.

[6] W. E. Buhro, A. T. Patton, C. E. Strouse, J. A. Gladysz, F. B. McCormick, M. C. Etter, *J. Am. Chem. Soc. 105* (1983) 1056.

1,3-Bis(tri-*tert*-butylsilyl)triazene**

By *Nils Wiberg**, *Gerd Fischer*, and *Petros Karampatses*

Whereas silyl derivatives of diazene **1**[1] and 2-tetrazene **3**[2] are well known, our attempts to synthesize silyl derivatives of the triazene **2**, a previously non-isolable nitrogen

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[**] Silicon Compounds, Part 56.—Part 55: N. Wiberg, G. Wagner, *Angew. Chem. 95* (1983) 1027; *Angew. Chem. Int. Ed. Engl. 22* (1983) 1005.

hydride of the series N_nH_n ("polyazenes"), were long unsuccessful[3].

HN=NH (1) HN=N–NH$_2$ (2) H$_2$N–N=N–NH$_2$ (3)

In each case instead of a silyltriazene, only its thermolysis products dinitrogen and silylamines were found[4].

$$\{R_3Si\text{–}N{=}N\text{–}N\} \longrightarrow N{\equiv}N + R_3Si\text{–}N \quad (a)$$

We have now succeeded for the first time in preparing a silylated triazene stable up to 150 °C—1,3-bis(tri-*tert*-butylsilyl)triazene **4**—by treating tri-*tert*-butylsilyl azide in tetrahydrofuran (THF) first with tri-*tert*-butylsilylsodium[5] and then with methanol.

$$t\mathrm{Bu_3Si\text{–}N{=}N{=}N} \xrightarrow[2)\ +\mathrm{MeOH},\ -\mathrm{NaOMe}]{1)\ +\mathrm{NaSi}t\mathrm{Bu_3}} t\mathrm{Bu_3Si\text{–}N{=}N\text{–}NH\text{–}Si}t\mathrm{Bu_3}$$

4

Apparently, the triazene decomposition is hindered in **4** by the extreme bulk of the two silyl substituents.

The novel compound **4** can be isolated as pale yellow crystals (m.p. = 139—140 °C, subl. = 110 °C/in vacuo), and was identified by elemental analysis, mass spectroscopy (molecular ion: *m/z* 441), and ^{1}H-NMR spectroscopy (90 MHz, C_6D_6; δ = 1.15, 1.28 (Si*t*Bu$_3$), 8.49 (NH); area ratio 27 : 27 : 1). The UV spectrum exhibits an intense $\pi_n \rightarrow \pi^*$ absorption band at $\tilde{\nu}_{max}$(hexane) = 38 600 cm^{-1} (ε = 15 900), which is also observed with other triazenes; however, an additional weak band appears at longer wavelength $\tilde{\nu}_{max}$(hexane) = 26 050 cm^{-1} (ε = 60), which is consistent with an $n \rightarrow \pi^*$ transition—in accord with earlier results[1], which show that the energy of the upper n level of an azo group is increased considerably by substitution of alkyl by silyl substituents—and indicates a comparably high energy for the n level in **4**.

From the coalescence of the proton resonance signals of the two *t*Bu$_3$Si groups of **4** at 55 °C (THF) it follows that the *N*-bonded hydrogen atoms migrates as shown in (b),

$$t\mathrm{Bu_3Si\text{–}N}\underset{\mathrm{N}}{\overset{\mathrm{H}}{\diagdown\!\!\diagup}}\mathrm{N\text{–}Si}t\mathrm{Bu_3} \rightleftharpoons t\mathrm{Bu_3Si\text{–}N}\underset{\mathrm{N}}{\overset{\mathrm{H}}{\diagdown\!\!\diagup}}\mathrm{N\text{–}Si}t\mathrm{Bu_3} \quad (b)$$

4a **4b**

and that the free energy of activation of this 1,3-shift is 78 kJ/mol at 55 °C, corresponding to an average lifetime of the tautomers of ca. 1/8 s. **4** decomposes above 150 °C, inter alia by elimination of N_2, as shown in (a), to afford bis(tri-*tert*-butylsilyl)amine.

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CAS Registry numbers:
4, 88211-13-6; *t*-Bu$_3$Si-N=N=N, 69322-38-9.

[1] N. Wiberg, *Angew. Chem. 83* (1971) 379; *Angew. Chem. Int. Ed. Engl. 10* (1971) 374.
[2] N. Wiberg, S. K. Vasisht, H. Bayer, R. Meyers, *Chem. Ber. 112* (1979) 2718; *113* (1980) 2916.
[3] Cf. H. J. Pracht, Dissertation, Universität München 1971, p. 71—80; N. Wiberg, W.-C. Joo, *J. Organomet. Chem. 22* (1970) 333, 341, 349.
[4] Silylated methyl- or phenyltriazenes of the type MeN=N–NMe(SiR$_3$) or PhN=N–N(SiR$_3$)$_2$ could, however, be obtained: N. Wiberg, H. J. Pracht, *Chem. Ber. 105* (1972) 1377, 1388, 1392, 1399; *J. Organomet. Chem. 40* (1972) 289.
[5] The previously unknown reagent NaSi*t*Bu$_3$ was obtained from *t*Bu$_3$SiBr and Na wire in refluxing THF. After removal of the solvent a colorless substance remains, which according to ^{1}H-NMR contains two molecules of THF per sodium atom (assumed formula $[Na(THF)_4]^{\oplus}[Na(Si\mathit{t}Bu_3)_2]^{\ominus}$.

Preparation of Enantiomerically Pure Chiral Alcohols by Asymmetric Alkylation of Glycolates**

By *Günter Helmchen** and *Reiner Wierzchowski*

Dedicated to Professor Karl Winnacker on the occasion of his 80th birthday

The propionates **1c** and **2c** of the chiral reagents **1a** and **2a**, which are readily accessible[1c] from (+)-camphor, can be alkylated with very high diastereoselectivity via lithium enolates[1]. We have now found that this also applies for *O*-protected glycolates such as **1b** and **2b**[2], but, compared to the propionates, a completely different mechanism is involved.

On metalation (−80 °C) with lithium cyclohexylisopropylamide (LICA) in tetrahydrofuran (THF) (conditions A), propionates yield highly selectively (*Z*)-enolates, but in THF-hexamethylphosphoric acid triamide (HMPT) (4 : 1) (conditions B) preferably give (*E*)-enolates[1c], alkylation of which yields products with inverse configuration at C-2′. In contrast, with *O*-benzylglycolates **1b** and **2b** we obtained almost identical product ratios under both conditions (Table 1). If front-side attack of the electrophile R^2–I and an enolate conformation [H–(C-2)–O–(C-1′)–O grouping] corresponding to the given formulas is as-

Table 1. Conversion of the esters **1b** and **2b** with alkylating agents R^2–I *via* lithium enolates into the esters **5** and **6**, and reduction of the dominant diastereoisomer in each case with LiAlH$_4$ (THF) to the alcohols **7**. Metalation: LICA (−80 °C) in THF (A) or THF-HMPT 4 : 1 (B); alkylation at −63 to −40 °C (A), −63 °C (B).

Educt	R^2	Solvent	Diastereoselectivity *ds* [%] [a]	Main Product	**5/6** Yield [%] [b]	**7** Yield [%] [c]	**7** Config.
1b	C_2H_5	A	87.5	(2′*R*)-**5b**	80 (94)	—	
1b	C_2H_5	B	92.5	(2′*R*)-**5b**	86	95 [d]	(−)(*R*)
2b	CH_3	A	88	(2′*S*)-**6a**	—	—	
2b	CH_3	B	91	(2′*S*)-**6a**	97	95	(+)(*S*) [e]
2b	C_2H_5	A	88	(2′*S*)-**6b**	75 (88)	—	
2b	C_2H_5	B	94.5	(2′*S*)-**6b**	86 (87)	95 [f]	(+)(*S*)
2b	n-$C_{10}H_{21}$	A	91	(2′*S*)-**6c**	82 (95)	—	
2b	n-$C_{10}H_{21}$	B	93	(2′*S*)-**6c**	82 (98)	96 [g]	(+)(*S*)

[a] Definition, see [2b]. [b] Total yield of chromatographically (MPLC) pure isolated esters **5** or **6**; values in brackets: yields corrected, since educt partially recovered. [c] Yields referred to diastereomerically pure **5** or **6**. [d] $[\alpha]_D^{21}$ −21.4° (*c* = 5.5, benzene), $[\alpha]_{15}^{22}$ −24.2° (*c* = 2.6, benzene); M. Asami, T. Mukaiyama, *Chem. Lett. 1983*, 93: $[\alpha]_D^{23}$ −16.55 (*c* = 5.07, benzene) for (*R*)-**7b**. [e] 3,5-Dinitrobenzoate: $[\alpha]_D^{26}$ +35.7° (*c* = 2.44, benzene); cf. K. Mislow, R. E. O'Brien, H. Schaefer, *J. Am. Chem. Soc. 84* (1962) 1940: $[\alpha]_D^{29}$ +35° (*c* = 2.0, benzene) for the 3,5-dinitrobenzoate of (+)(*S*)-**7a**. [f] $[\alpha]_D^{22}$ +24.2° (*c* = 2.4, benzene). [g] $[\alpha]_D^{20}$ +17.5° (*c* = 1.0, chloroform); cf. C. Fuganti, P. Grasselli, S. Servi, *J. Chem. Soc. Chem. Commun. 1982*, 1285: $[\alpha]_D^{20}$ +17.1° and −17.5° (*c* = 1.1, chloroform) for (+)(*S*)- and (−)(*R*)-**7c**, resp. (concentration: private communication *S. Servi*).

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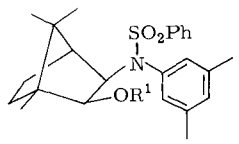
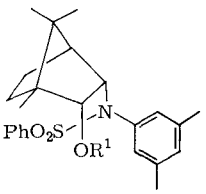
sumed (cf. [1b,c]), it follows from the configuration (C-2′) of each of the dominant products, (2′*R*)-**5b** and (2′*S*)-**6a–c**, respectively, that the enolates **3a** and **4a** are present in the (*E*)-configuration. The preferential formation of the same enolate[3] under both conditions was confirmed in the case of **1b** by reaction of the enolate **3a** with *tert*-butyldimethylsilyl chloride (−63-0 °C) to give the ketene acetal **3b** of ca. 90% purity[4], according to a ^{1}H-NMR spectroscopic analysis.



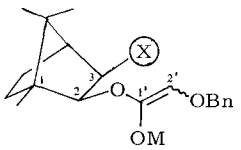
1



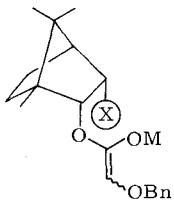
2

a, R^1 = H; **b**, R^1 = $COCH_2OBn$; **c**, R^1 = $COCH_2CH_3$

3a, b

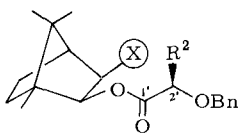


4a

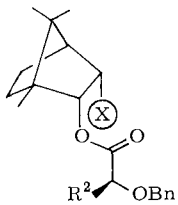


a, M = Li; **b**, M = $Si(CH_3)_2tBu$

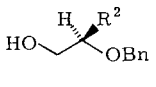
5b



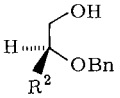
6a-c



a, R^2 = CH_3; **b**, R^2 = C_2H_5; **c**, R^2 = n-$C_{10}H_{21}$

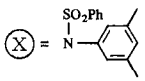


(*R*)-**7b**



(*S*)-**7a-c**

Bn = Benzyl



The main products (2′*R*)-**5b** and (2′*S*)-**6a–c** can in each case be readily separated preparatively from the C-2′ epimers by medium pressure liquid chromatography (MPLC) and are crystalline; on reduction ($LiAlH_4$/THF) they yield the alcohols **7**, which are presumably enantiomerically pure, since the esters are known to be reduced by $LiAlH_4$ without racemization; furthermore, optical rotations in the case of **7a** and **7c** agree with reliable reference values.

Partially protected 1,2-diols **7** are versatile building blocks for natural product syntheses. Furthermore, it should be noted that glycolate alkylations are "umgepolt" relative to aldol additions regarding the hydroxylated C-atom; that is, glycolates **1b** and **2b** are d^1-ethanol synthetic equivalents[5] which open up interesting possibilities for syntheses with "acyclic control of stereochemistry".

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[1] a) E. Ade, G. Helmchen, G. Heiligenmann, *Tetrahedron Lett. 21* (1980) 1137; b) R. Schmierer, G. Grotemeier, G. Helmchen, A. Selim, *Angew. Chem. 93* (1981) 209; *Angew. Chem. Int. Ed. Engl. 20* (1981) 207; c) G. Helmchen, A. Selim, D. Dorsch, I. Taufer, *Tetrahedron Lett. 24* (1983) 3213.

[2] a) Reactions of achiral glycolate-enolates with electrophiles have been described by several groups; see *e.g.* G. Stork, A. Schultz, *J. Am. Chem. Soc. 93* (1971) 4074; b) for asymmetric syntheses with lithium enolates of cyclic ester-acetals of α-hydroxy acids (lactic acid, mandelic acid), which, however, are only suitable for the synthesis of specific optically active tertiary alcohols, see D. Seebach, R. Naef, *Helv. Chim. Acta 64* (1981) 2704; G. Frater, U. Müller, W. Günther, *Tetrahedron Lett. 22* (1981) 4221.

[3] On the basis of the Ireland-Claisen rearrangement, the (*E*)-configuration was likewise postulated for lithium enolates of *O*-benzyllactic and -mandelic acid esters; P. A. Bartlett, D. J. Tanzella, J. F. Barstow, *J. Org. Chem. 47* (1982) 3941. Current investigations in our laboratory (F. Wirsing, Diplomarbeit, Würzburg 1983) show that on metalation in THF the (*E*)-configuration is not the rule, but only preferred for certain *O*-protecting groups.

[4] Characteristic signals: (δ-values, 400 MHz, $CDCl_3$, 5°C): 0.18 [s, 6H, $Si(CH_3)_2$], 0.96 (s, 9H, *t*Bu), 4.68/4.72 (AB, J = 11.7 Hz, 2H, OCH_2), 5.87 (s, 1H, 2′-H). The signals of the minor silylketene acetal cannot yet be assigned with certainty.

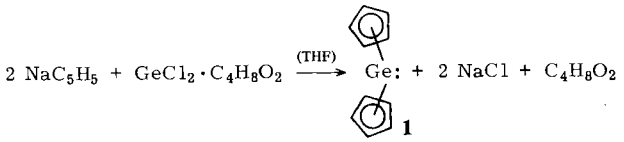
[5] D. Seebach, *Angew. Chem. 91* (1979) 259; *Angew. Chem. Int. Ed. Engl. 18* (1979) 239.

Novel Structures Containing Germanium(II): Germanocene and Dimeric Tricarbonyl(di-*tert*-butoxygermylene)nickel(0)**

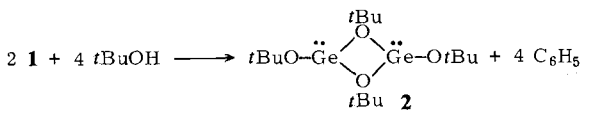
By *Mario Grenz, Ekkehardt Hahn, Wolf-Walther du Mont**, and *Joachim Pickardt*

Previously, the coordination chemistry of "carbene analogues" has principally been considered under the aspect "stabilization of low valent species" in the coordination sphere of metal acceptors. We now describe for the first time the structure of a complex that formally appears analogous to the carbene complexes, but which is not sufficiently "internally" stabilized and hence dimerizes *via* heteroatom bridging. Until now, heteroatom bridged structures have only been proposed for some functionally substituted stannylene complexes with associated tin(II) ligands such as *e.g.*, $[Cr(CO)_5Sn(OH)_2]_x$, $[Cr(CO)_5Sn(OMe)_2]_x$, and $[Ni(CO)_3Sn(OtBu)_2]_2$[1]; corresponding complexes containing germanium(II) ligands were previously unknown.

We obtained the first complex with a $Ge(OR)_2$ ligand by cleavage of germanocene **1** with *tert*-butyl alcohol and allowing the di-*tert*-butoxygermanium(II) **2** thus formed to react with tetracarbonylnickel.



1



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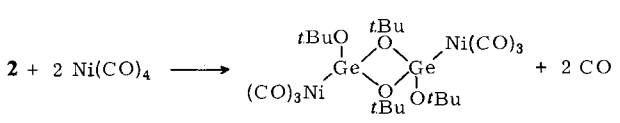

3

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Technischen Universität Berlin

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

In contrast to reports in the literature, we were able to prepare germanocene **1**, which is described as monomeric in solution but polymeric in the solid state[2–4], in tetrahydrofuran (THF) from sodium cyclopentadienide and the dichlorogermanediyl-dioxane adduct. Colorless crystals of **1** (m.p. = 78 °C) were isolated by sublimation at 10^{-2} mbar (bath temperature 60–80 °C) in 60% yield. The compound is so stable that it can be manipulated like stannocene under an inert gas atmosphere, and can be stored in the refrigerator (−30 °C) for several weeks without noticeable polymerization. Sublimed germanocene crystallizes orthorhombically; the X-ray structure analysis (Fig. 1) establishes that **1** is monomeric and for the first time provides a reliable value for the angle of aperture of the cyclopentadienyl ring planes in germanocene derivatives[5]: 50.4° for **1** contrasted with 45.9 or 48.4° for stannocene[6]. The deviation from a metallocene structure of the D_{5d} or D_{5h} type is therefore larger in germanocene than in stannocene (with the larger central atom!). Remarkable also is the nonequivalence of the Ge–C distances (234.7 to 273.0 pm), which can be described as a displacement of the germanium atom from the point of intersection of the fivefold axis towards the apex at which the Cp ring planes touch. This effect is even more pronounced in **1** than in stannocene and decamethylstannocene[6, 7].

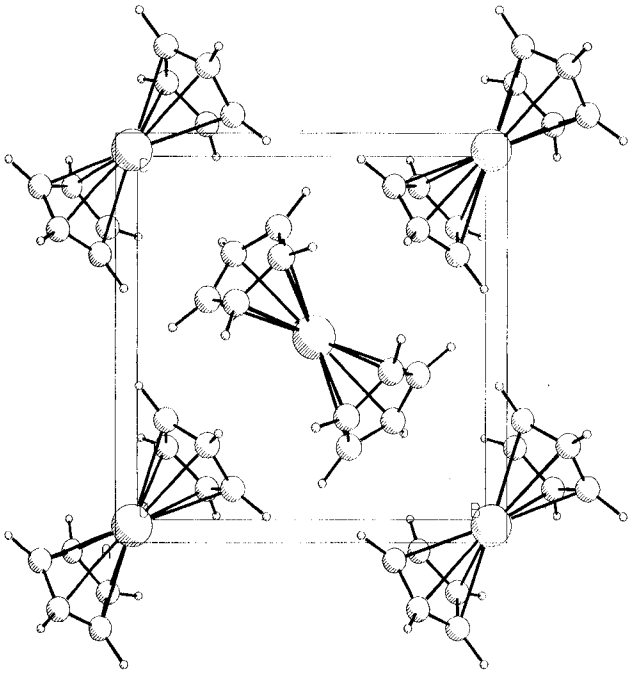

Fig. 1. PLUTO representation of the structure of germanocene **1** in the crystal. Orthorhombic, $P22_12_1$ (nonstandard representation of $P2_12_12$, No. 18), $a = 561.7(28)$, $b = 886.0(19)$, $c = 888.8(30)$ pm, $V = 442.3 \times 10^6$ pm^3, $Z = 2$; $Mo_{K\alpha}$, $2\theta \leq 60°$, solved using Patterson methods, refined (SHELX, anisotropic H atoms with constant temperature factor 8.0×10^4 pm^2) to $R = 0.042$ with 779 reflections with $I > 2\sigma_I$. Important distances [pm]: Ge–C1 258.4(7), Ge–C2 234.7(7), Ge–C3 235.9(6), Ge–C4 256.6(6), Ge–C5 273.0(7), C–C 134.7(12) to 140.2(12) (standard deviations in parenthesis). Data collected at −100(5) °C [10].

Even in the absence of bulky substituents on the cyclopentadienyl rings, **1** is apparently stable enough as a monomer to serve as an excellent educt for the synthesis of Ge^{II} compounds. Hence, alcoholysis of **1** with *t*BuOH affords dimeric "germylene" **2** with a four-membered ring structure, which is also accessible analytically pure by salt elimination methods and multiple recrystallizations[8]. **2** reacts with dimethylbutadiene via typical 1,4-cycloaddition of the carbene-analogous monomeric $Ge(OtBu)_2$[3], and with tetracarbonylnickel *via* CO-elimination to afford dimeric tricarbonyl(di-*tert*-butoxygermylene)nickel(0) **3**. Complex **3** is formed practically quantitatively (NMR), and at −30 °C precipitates out from pentane as colorless crystals (m.p. = 136 °C (decomp.)).

As indicated by the X-ray structure analysis (Fig. 2), **3** contains two *tert*-butyloxo bridges between the coordinating germanium atoms of a bidentate "1,3,2,4-dioxadigermetane" ligand, which is isoelectric with *trans*-diazadiphosphetidines. The transition-metal coordination arises from the 4s electron lone-pair of the "soft" germanium atom. The configuration of the bonds at the tetra-coordinated Ge atoms in **3** deviate markedly from tetrahedral: the OGeO angles are small (74.9 and 95.5°); in contrast, all NiGeO angles are larger than 119° (Fig. 2). The distance

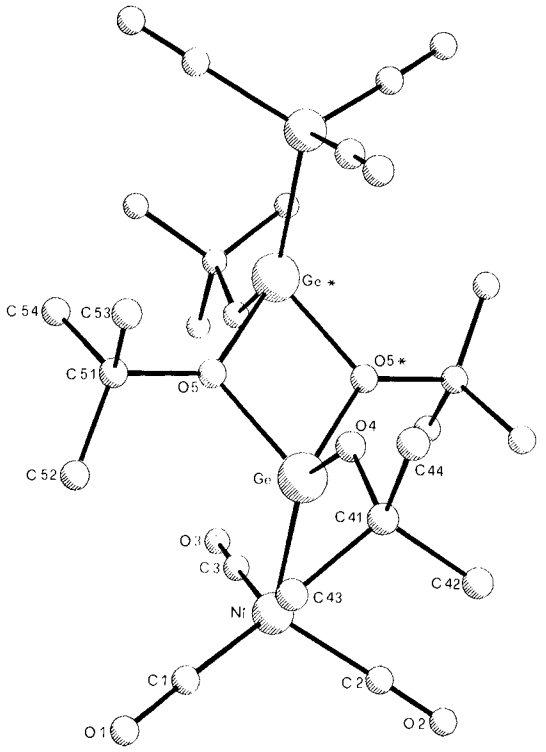

Fig. 2. PLUTO representation of the structure of the binuclear nickel complex **3** in the crystal. For preparation of the crystal cf. [10], data collection at −100(5) °C. Triclinic, $B\bar{1}$ (nonstandard representation of $P\bar{1}$, No. 2, selected because of orthogonality of the cell), $a = 1568.4(41)$, $b = 1028.1(21)$, $c = 1020.5(22)$ pm, $\alpha = 109.69(16)$, $\beta = 91.75(21)$, $\gamma = 89.54(19)°$, $V = 1548.6 \cdot 10^6$ pm^3, $Z = 2$. $Mo_{K\alpha}$, $2\theta \leq 40°$, solved using Patterson methods, refinement (SHELX, anisotropic, CH_3 as rigid group) to $R = 0.055$ with 134.1 reflections with $I > 2\sigma_I$. Most important distances [pm]: Ge–Ni 228.3(2), Ge–$O_{term.}$ 178.0(6), Ge–$O_{br.}$ 193.2(6) and 192.1(6), Ge···Ge 305.9(2).

Ge–Ni is shorter than the sum of the covalent radii as in monomeric germylene complexes, which are closely analogous to carbene complexes, and for which Ge-metal bond orders of up to 1.5 have been proposed[9].

Transition-metal coordination of germanediyls (germylenes), therefore, does not necessarily lead to a preference for structures analogous to those of carbene- or μ-methylene-complexes. We therefore expect that more highly associated Ge^{II} compounds will also exhibit ligand properties. The CO stretching frequencies of **3** (2070, 2000 cm^{-1}) indicate electronic ligand parameters that make O-bridged Ge^{II} compounds comparable to conventional P ligands.

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1, 39366-46-6; **2**, 88271-73-2; **3**, 88271-74-3.

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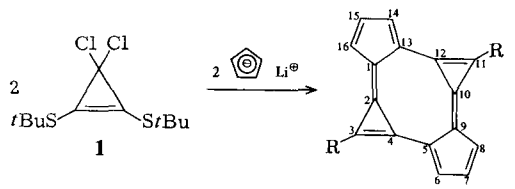
A Novel Aromatic Hydrocarbon with 16π-Electron Periphery: "Cyclic Bicalicene"

By *Shigeo Yoneda, Mitsuhiro Shibata, Shuji Kida, Zen-ichi Yoshida*, Yasusi Kai, Kunio Miki,* and *Nobutami Kasai*

Polycyclic, nonalternant, peripheral 4nπ systems, which may be regarded as perturbated annulenes, should be antiaromatic if they have a planar conformation like pentalene and *s*-indacene[1]. This concept is well established. In contrast, an extremely interesting example of an aromatic, 4nπ system is pentacyclo[11.3.0.0^{2,4}.0^{5,9}.0^{10,12}]hexadeca-1,3,5,7,9,11,13,15-octaene **4** (cyclic bicalicene), which possesses a planar, peripheral 16π-electron structure, and was briefly described at the ISNA-4 conference (Jerusalem, 1981)[2]. Here, we report on novel chemical properties of **4** together with details of its synthesis and structure.

1,2-Bis(*tert*-butylthio)-3,3-dichlorocyclopropene **1** was treated with 2 equiv. lithium cyclopentadienide in tetrahydrofuran at −78 °C for 2 h. The reaction mixture was then chromatographed on silica gel with dichloromethane-petroleum ether and subsequently recrystallized from 1,2-dimethoxyethane to give the 3,11-bis(*tert*-butylthio) derivative **2** (reddish purple crystals, m.p. = 190–200° (dec.), 5% yield). Desulfurizing stannylation of **2** with tri-*n*-butyltin hydride in refluxing benzene in the presence of azoisobutyronitrile gave the 3,11-bis(tri-*n*-butylstannyl) derivative **3** (orange crystals, m.p. = 60–61 °C, 42%). Subsequent treatment of **3** with silica gel (Kieselgel 60PF$_{254}$ Merck) afforded hydrocarbon **4** (orange crystals, m.p. = 125–130 °C (dec.), 40%). **4** is stable for several weeks in air at room temperature.



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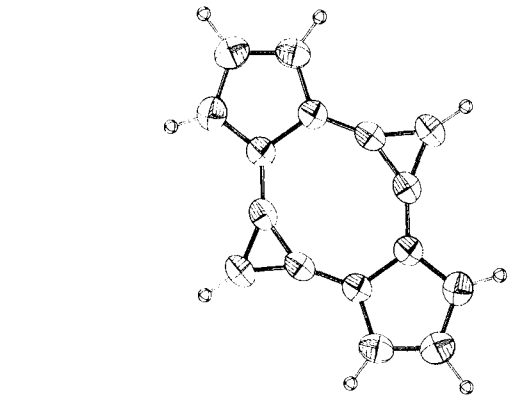
As indicated by the X-ray structure analysis (Fig. 1), **4** possesses a planar ring skeleton and no bond alternation is observed (D_{2h} symmetry). The ^{1}H-NMR signals of **4** exhibit no upfield shift due to the paramagnetic ring current expected from the 16π system (Table 1), indicating that the



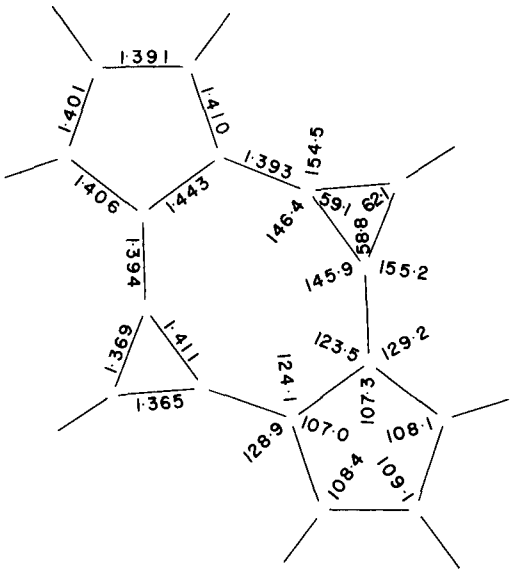


Fig. 1. Molecular structure of **4** in the crystal, 30% probability ellipsoids (top) bond distances and angles (standard deviation 0.002 to 0.003 Å) (bottom). **4** is monoclinic, space group $P2_1/c$, $a = 9.587(1)$, $b = 5.964(1)$, $c = 9.968(1)$ Å, $\beta = 117.01(1)°$, $V = 507.7(1)$ Å^3, $Z = 2$, $\varrho_{X\text{-ray}} = 1.309$, $\varrho_{obs.} = 1.30$ g cm^{-3}, reflections with ($|F_0| > 3\sigma(F_0)$), $R = 0.039$.

Table 1. Spectroscopic data for **2** and **4**.

	2	**4**
IR (KBr), [cm^{-1}]	1815, 1555	1782, 1550
UV (CH_2Cl_2) λ_{max} [nm] (lg ε)	239 (4.51), 266 (4.49), 337 (4.74), 372 (4.43), 413 (4.39), 525 (2.74)	241 (4.63), 328 (4.51), 390 (4.27), 470 (2.81)
^{1}H-NMR [a, b]	1.75 (s, 18H, *t*Bu), 6.40 (t, 2H, H-7,15, J = 3.8 Hz), 6.87 (d, 4H, H-6,8,14,16, J = 3.8 Hz)	6.58 (t, 2H, H-7,15, J = 3.7 Hz), 7.11 (d, 4H, H-6,8,14,16, J = 3.7 Hz), 7.91 (s, 2H, H-3,11)
^{13}C-NMR [a, c]	31.6 ($C(CH_3)_3$), 48.0 ($C(CH_3)_3$), 109.0 (C-1,5,9,13), 123.0 (C-7,15, J = 170.6 Hz), 127.5 (C-6,8,14,16), J = 165.5 Hz), 128.2 (C-3,11), 135.9 (C-2,4,10,12)	110.2 (C-1,5,9,13), 117.8 (C-3,11, J = 235.5 Hz), 124.7 (C-7,15, J = 164.4 Hz), 130.5 (C-6,8,14,16, J = 167.9 Hz), 140.9 (C-2,4,10,12)

[a] **2** in $CDCl_3$, **4** in CD_2Cl_2. [b] 100 MHz, 25 °C. [c] 90 MHz, 25 °C; coupling constants, $J_{^{13}C\text{-}H}$.

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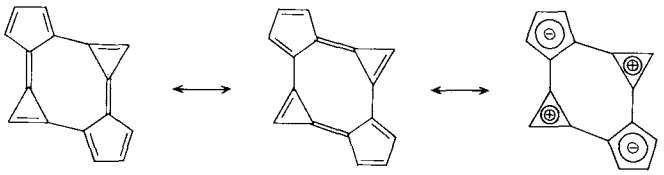
[16]annulene structure does not contribute to its ground state. Also, the percent resonance energy of **4** (0.87) is larger than the aromatic criterion (0.50) defined by *Aihara*[3]. In view of these results, **4** is to be regarded as a peripheral 16π aromatic system.

The charge distribution on each C atom of **4** estimated from the ^{13}C-NMR spectrum is in accord with the calculated charge distribution (MINDO/3, net charge density: C-1,13 −0.12, C-14,16 +0.02, C-15 −0.08, C-2,4 +0.16, C-3 −0.09). These results demonstrate that the negative charge is mainly distributed over C-1,13,15 and the positive charge over C-2,4. We therefore conclude that **4** is stabilized by the resonance of two covalent structures (**4a** and **4b**) and one polarized structure (**4c**) in which the five-membered ring is similar to the cyclopentadienide anion and three-membered ring, similar to the cyclopropenylium cation[4].



4a **4b** **4c**

The chemical properties of this system are consistent with the π-configuration of **4**. Thus, in agreement with no contribution from the peripheral [16]annulene structure, electrochemical or alkali metal reduction of **4** leads to decomposition, in marked contrast to [16]annulene which gives the 18π system by two electron reduction[5]. Also, the HOMO energy level of **4** (MINDO/3) is extremely high (−7.22 eV), suggesting that it should be a good electron donor. On the other hand, although reaction of **4** with $NO^+_2BF^-_4$ and with CF_3COOH affords undefined products (no characteristic absorption of calicene in IR spectra at ca. 1800 and ca. 1550 cm^{-1}), reaction of **4** with *N*-bromosuccinimide in dichloromethane proceeds smoothly to afford the 6,7,8,14,15,16-hexabromo derivative (orange crystals, m.p. = 222–225 °C (dec.), 80%). Nucleophilic substitution of **2** with diethylamine in dichloromethane gives the 3-*tert*-butylthio-11-diethylamino derivative **6** (dark reddish-purple crystals m.p. = 116–117 °C, 36%).

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1, 72649-41-3; **2**, 72649-42-4; **3**, 73625-08-8; **4**, 73091-52-8; **4** (hexabromo deriv.), 88245-24-3; *4* (3-*tert*-butylthio-11-diethylamino deriv.), 88245-25-4; lithium cyclopentadienide, 16733-97-4; tributyltin hydride, 68-73-3.

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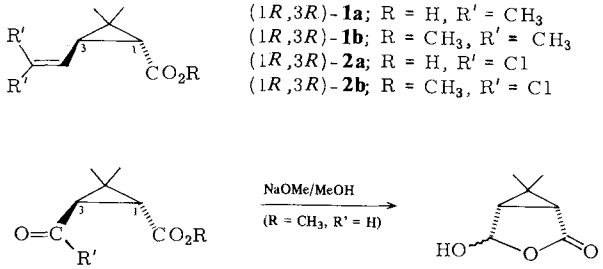
Enzymatic Syntheses of Chiral Building Blocks from Racemates: Preparation of (1*R*,3*R*)-Chrysanthemic, -Permethrinic and -Caronic Acids from Racemic, Diastereomeric Mixtures**

By *Manfred Schneider**, *Norbert Engel*, and *Heike Boensmann*

The physiological activities of pyrethroid insecticides derived from chrysanthemic acid (1*R*,3*R*)-**1a** and permethrinic acid (1*R*,3*R*)-**2a** are closely related to their absolute configurations, making the 1*R*-enantiomers interesting targets for organic synthesis. Important chiral building blocks for the synthesis of optically active pyrethroids are also the caronic acid derivatives (1*R*,3*R*)-**3a** and -**3c** to -**3e**[1]. Simple methods for the preparation of (1*R*,3*R*)-**1a** to -**3a** starting from readily available educts therefore provide an interesting synthetic challenge.



(1*R*,3*R*)-**1a**; R = H, R' = CH_3
(1*R*,3*R*)-**1b**; R = CH_3, R' = CH_3
(1*R*,3*R*)-**2a**; R = H, R' = Cl
(1*R*,3*R*)-**2b**; R = CH_3, R' = Cl

(1*R*,3*R*)-**3a**; R = CH_3, R' = OH
(1*R*,3*R*)-**3b**; R = CH_3, R' = OCH_3
(1*R*,3*R*)-**3c**; R = CH_3, R' = O*t*Bu
(1*R*,3*R*)-**3d**; R = CH_3, R' = H
(1*R*,3*R*)-**3e**; R = *t*Bu, R' = H

4

In contrast to well documented asymmetric syntheses[2] and the resolution of racemic mixtures[1,2], the potential of enzymatic reactions has never been tested in this context. In fact diastereomeric, racemic mixtures of the methyl esters **1b** to **3b** are readily hydrolyzed enzymatically in the presence of porcine liver esterase (Scheme 1). **1b** to **3b** (10–200 mmol) are suspended in 0.1 M phosphate buffer (pH 8) and mixed with the esterase [ca. 70 units (standard ethyl butyrate) = 0.7 mg/g substrate]. The initial enzymatic saponification is indicated by the decrease of pH, which is maintained at pH 8 by the addition of 1 N NaOH solution from an automatic buret. The reactions can be monitored from the consumption of NaOH and can be interrupted after the desired conversion (e.g. 50%). The unreacted esters are removed from the reaction mixtures by extraction (Et_2O). The acids formed, which are present in the aqueous phase as sodium salts, are isolated after acidification to pH 2 by continous extraction with Et_2O. Diastereomeric ratios of all fractions were determined by gas chromatography, and the enantiomeric ratios determined by ^{1}H-NMR spectroscopy and/or gas chromatographic analysis of the diastereomeric (−)-menthyl esters.

The products (1*R*,3*R*)-**1a** to -**3a** can indeed be obtained in good yields with the enantiomeric ratios listed in Table

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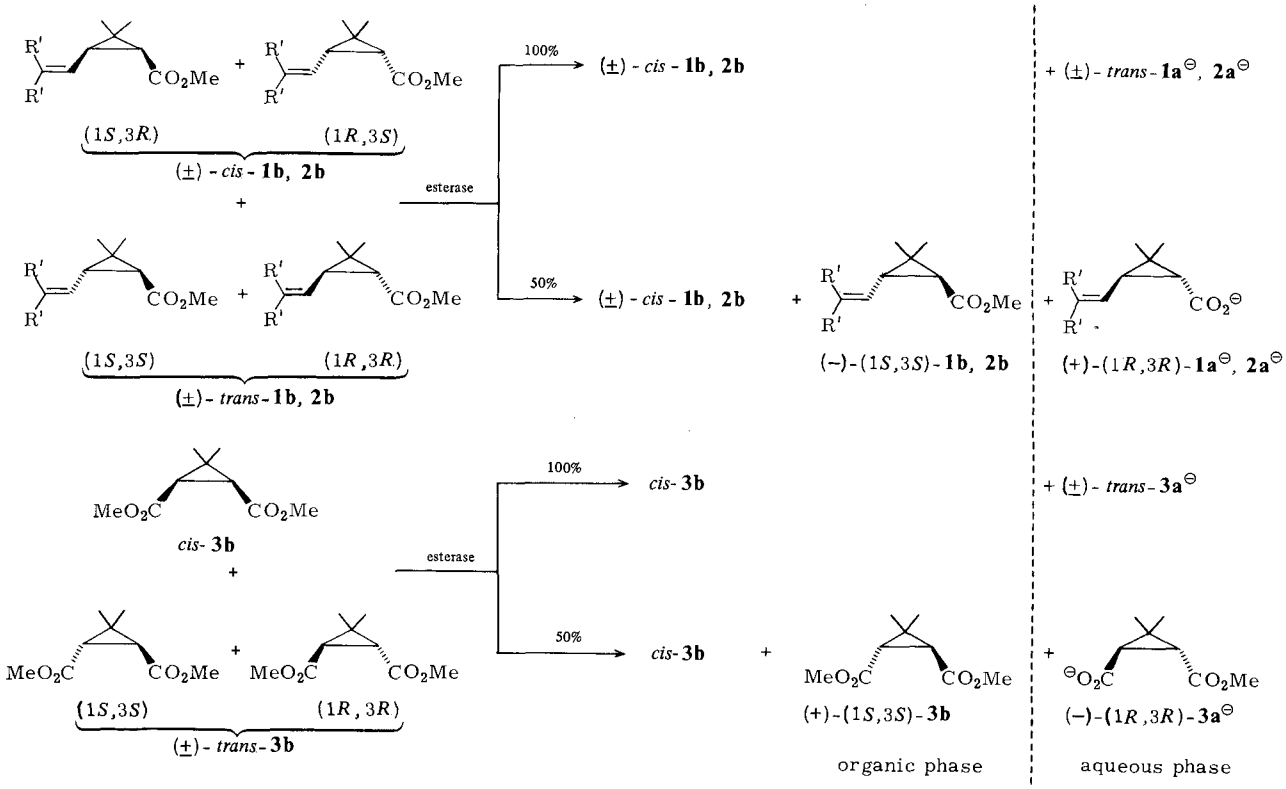

Scheme 1. Diastereoselective enzymatic hydrolysis of **1b** [R′ = CH_3; (±)-*cis*-**1b** : (±)-*trans*-**1b** = 23 : 77], **2b** [R′ = Cl; (±)-*cis*-**2b** : (±)-*trans*-**2b** = 14 : 86] and **3b** [*cis*-**3b** : (±)-*trans*-**3b** = 20 : 80] as well as enantioselective enzymatic hydrolysis of *trans*-**1b** to -**3b** at 25 °C. Enzyme: porcine liver esterase.

Table 1. Enzymatic hydrolysis of the methyl esters **1b-3b**.

Substrate	Conditions [a]	Product	Yield [%] [b]	*R*:*S* [c]
cis,trans-**1b**	A (50)	(1*R*,3*R*)-**1a**	90	70 : 30
trans-**1b**	A (50)	(1*R*,3*R*)-**1a**	85	73 : 27
		(1*S*,3*S*)-**1b**	80	30 : 70
trans-**1b**	A (30)	(1*R*,3*R*)-**1a**	75	80 : 20
(+)-(1*R*,3*R*)-**1b**	B (50)	(1*R*,3*R*)-**1a**	75	85 : 15
cis,trans-**2b**	A (50)	(1*R*,3*R*)-**2a**	90	90 : 10
(+)-(1*R*,3*R*)-**2a**	C	(1*R*,3*R*)-**2a**	65	98 : 2 [d]
cis,trans-**3b**	A (50)	(1*R*,3*R*)-**3a**	85	80 : 20
trans-**3b**	A (50)	(1*R*,3*R*)-**3a**	85	80 : 20
		(1*S*,3*S*)-**3b**	90	25 : 75
(−)-(1*R*,3*R*)-**3a**	C	(1*R*,3*R*)-**3a**	65	91 : 9 [d]
(−)-(1*R*,3*R*)-**3b**	B (60)	(1*R*,3*R*)-**3a**	70	97 : 3

Product	250 MHz ^{1}H-NMR [e]
(1*R*,3*R*)-**1a**	1.16 (s, 3H, CH_3), 1.31 (s, 3H, CH_3), 1.40 (d, 1H), 1.73 (m, 6H, $2CH_3$), 2.11 (dd, 1H), 4.92 (m, 1H)
(1*R*,3*R*)-**2a**	1.23 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 1.64 (d, 1H), 2.30 (dd, 1H), 5.65 (d, 1H)
(1*R*,3*R*)-**3a**	1.32 (s, 3H, CH_3), 1.34 (s, 3H, CH_3), 2.27 (AB, 2H), 3.72 (s, 3H, CH_3)

[a] A = enzymatic hydrolysis (% conversion); B = A with recycling after esterification (% conversion); C = recrystallisations from petroleum ether, b.p. = 60–90 °C. [b] Based on converted substrate. [c] Determined by ^{1}H-NMR (with (+)-(*R*)-α-methylbenzylamine or Eu(tfc)$_3$) and GC (±5%). [d] Determined by calibrated GC (±2%). [e] δ-Values, solvent $CDCl_3$ *T* = 25 °C.

1. Clearly, the enzymatic reactions are both *diastereo-* and *enantioselective:*

a) *Diastereoselective hydrolysis:* At the enzyme concentrations used the *cis*-methyl esters (*cis*-**1b** to -**3b**) are not accepted by the enzyme as substrates. They can be recovered unchanged from the reaction mixtures. In contrast, *trans*-**1b** to -**3b** are readily saponified by the enzyme under these conditions. Complete conversions therefore achieve a separation of the *cis*- and *trans*-cyclopropane derivatives (Scheme 1).

b) *Enantioselective hydrolysis:* Enzymatic hydrolysis of *trans*-**1b** to -**3b** at lower conversions (e.g. 50%), produces, after removal of the unreacted (1*S*,3*S*)-**1b** to -**3b**, the optically active acids (1*R*,3*R*)-**1a** to -**3a** (Scheme 1, Table 1). The desired 1*R*-enantiomers are saponified much faster.

The, as yet non-optimized, enantiomeric ratios can be further increased by the usual methods (lower conversion, recycling, recrystallization; cf. examples in Table 1). Chrysanthemic acid (1*R*,3*R*)-**1a** ($[\alpha]_D^{22}$ 16, *c* 1.48, $CHCl_3$) can be obtained from the enzymatic process in 70% *ee*. In contrast, permethrinic acid (1*R*,3*R*)-**2a** ($[\alpha]_D^{25}$ 32.7, *c* 0.86, $CHCl_3$), which is of particular commercial interest, can be obtained almost enantiomerically pure (98 ± 2% (GC), 96% *ee*) after one recrystallization (petroleum ether) of the initial product (80% *ee*). Caronic acid monomethyl ester (−)-(1*R*,3*R*)-**3a** is obtained almost enantiomerically pure (97 ± 2% (GC), 95% *ee*). This ester is not easily accessible by other methods[1,2]. It can also be converted into other building blocks[1] such as (1*R*,3*R*)-**3c** [^{1}H-NMR: δ = 1.28 (s, 6H, $2CH_3$), 1.46 (s, 9H, *t*Bu), 2.16 (bs, 2H), 3.70 (s, 3H, OCH_3); $[\alpha]_D^{25}$ −20.7, *c* 1.07, $CHCl_3$] and (1*R*,3*R*)-**3d** [^{1}H-NMR: δ = 1.32, 1.35 (s, 3H, CH_3), 2.49 (AB, 2H), 3.73 (s, 3H, OCH_3), 9.66 (d, 1H); $[\alpha]_D^{25}$ 15, *c* 1.43, $CHCl_3$]. (1*R*,3*R*)-**3d** can be converted via a known procedure[1,2] into **4**, thereby allowing a synthetic entry into the corresponding *cis*-series.

The chosen reaction times (8-72 h) are dependent on the amounts of substrate and enzyme and depent on the specific activities (10^{-6} mol min^{-1} (mg enzyme)$^{-1}$) [(+)-(1*R*,3*R*)-**1a**: ca. 1.0 (+)-(1*R*,3*R*)-**2a**: ca. 1.7; (−)-(1*R*,3*R*)-**3a**: ca. 7; standard (ethyl butyrate): 100)] of the enzyme towards the substrates, which were determined with the enantiomerically pure (enriched) materials.

The studies are also interesting with respect to enzyme-substrate relations and "in vitro"-investigations of insecticide metabolism in mammals[3].

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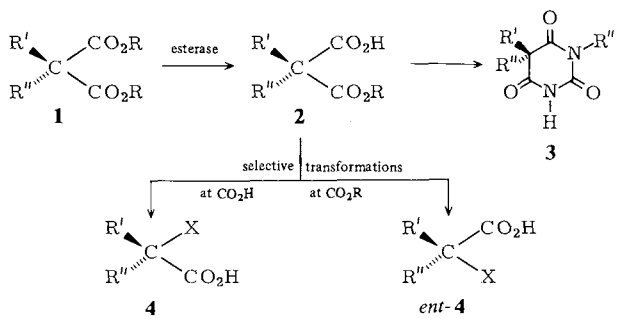
Enzymatic Synthesis of Chiral Building Blocks from Prochiral Substrates: Enantioselective Synthesis of Monoalkyl Malonates**

By *Manfred Schneider**, *Norbert Engel*, and *Heike Boensmann*

Enantioselective conversion of the prochiral dialkyl malonates **1** into their chiral monoesters **2** would produce versatile building blocks for numerous other optically active molecules. Selective transformations (derivatization, degradations, reductions etc.) of the two, now chemically distinguishable, functional groups at the chiral center in **2** would allow optional entry to *both* enantiomeric series of potential target molecules. Optically active barbiturates **3** or α-amino acids **4**/*ent*-**4** (X = NH_2) are examples of possible synthetic applications. A simple method for the enantioselective conversion of the readily accessible, prochiral precursors **1** would therefore be very useful, regardless of the resulting absolute configurations of the products **2**.



1 **2** **3** **4** *ent*-**4**

Enzymes are able to convert prochiral substrates enantioselectively into chiral molecules by enantiotopic group differentiation[1]. Hydrolytic enzymes from microorganisms were used several years ago to convert prochiral dialkyl glutarates into their chiral monoesters[2]. Porcine liver esterase was used in a similar way for a chemoenzymatic synthesis of (*R*)-mevalonolactone[3].

Since porcine liver esterase is easy to handle[4] and conveniently accessible it seemed attractive to use this enzyme for the conversions **1** → **2**. The dialkyl malonates **1a-1f** (10-50 mmol) were suspended in 0.1 N phosphate buffer (pH 8) and mixed with the esterase [70 units (standard: ethyl butyrate) = 0.7 mg/(g substrate)]. The initial enzymatic saponification is indicated by a decrease in pH, which is maintained at pH 8 by the addition of 1 N NaOH solution from an automatic buret. Only one ester group is saponified and the reaction terminates after the consumption of 1 equiv. of NaOH; the reaction mixtures become homogeneous. The monoesters **2a-2f** formed, which are present as sodium salts in the aqueous phase, are isolated in good yields after acidification to pH 2 by continous extraction (Et_2O). The enantiomeric ratios were determined by NMR spectroscopy of the crude products (Table 1).

Table 1. Enzymatic hydrolysis of dialkyl malonates **1** to the monoalkyl esters **2**.

	R′	R″	R	Enantiomer ratio [a]
a	*n*Bu	Me	Et	69 : 31
b	*n*Bu	Me	Me	75 : 25
c	Et	Me	Et	60 : 40
d	*n*Pr	Me	Et	54 : 46
e	Ph	Me	Et	93 : 7
f	Ph	Et	Me	92 : 8

[a] Determined by 250 MHz ^{1}H-NMR with (+)-(R)-α-methylbenzylamine.

From Table 1 it is clear that the enantioselectivities are dependent on the substitution pattern at the chiral centers of **2a-2f** and are largest when the difference in substituent size ΔR′R″ reaches a maximum. Methyl esters, which are preferable also due to their higher rates of hydrolysis, appear to give somewhat higher enantiomeric purities than ethyl esters. The best results from a synthetic point of view were obtained with **1e** and **1f**, which afforded the monoalkyl malonates **2e** and **2f**, respectively, in high enantiomeric ratios; these were further improved to >97:3 (NMR) by recrystallization.

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1a, 55114-29-9; **1b**, 88253-94-5; **1c**, 2049-70-9; **1d**, 55898-43-6; **1e**, 34009-61-5; **1f**, 88253-95-6; (*R*)-**2a**, 88293-58-7; (*S*)-**2a**, 88293-59-8; (*R*)-**2b**, 88253-96-7; (*S*)-**2b**, 88253-97-8; (*R*)-**2c**, 80226-12-6; (*S*)-**2c**, 42214-17-9; (*R*)-**2d**, 88253-98-9; (*S*)-**2d**, 88253-99-0; (*R*)-**2e**, 88254-00-6; (*S*)-**2e**, 88254-01-7; (*R*)-**2f**, 88254-02-8; (*S*)-**2f**, 88254-03-9; esterase, 9013-79-0.

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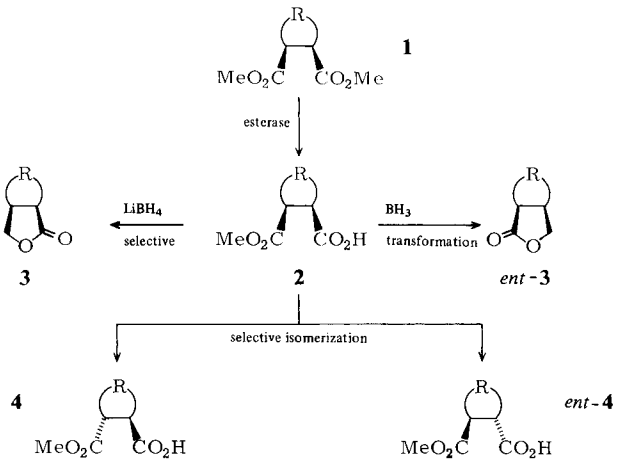
[1] D. Seebach, E. Hungerbühler, A. Fischli in R. Scheffold: *Modern Synthetic Methods*, Salle+Sauerländer, Aarau 1980; J. B. Jones, C. J. Sih, D. Perlman in A. Weissberger: *Techniques of Chemistry, Vol. 1, 2*, Wiley, New York 1975.
[2] H. Kosmol, K. Kieslich, H. Gibian, *Justus Ann. Chem. 711* (1968) 38.
[3] F.-C. Huang, L. F. Hsu Lee, R. S. D. Mittal, P. R. Ravikumar, J. A. Chan, C. J. Sih, E. Caspi, C. R. Eck, *J. Am. Chem. Soc. 97* (1975) 4144.
[4] M. Schneider, N. Engel, H. Boensmann, M. Schneider, N. Engel, P. Hönicke, G. Heinemann, H. Görisch, *Angew. Chem. 96* (1984) 52; *Angew. Chem. Int. Ed. Engl. 23* (1984) 64; *ibid. 96* (1984) 55; *23* (1984) 67.

Enzymatic Syntheses of Chiral Building Blocks from Prochiral *meso*-Substrates: Preparation of Methyl(hydrogen)-1,2-cycloalkanedicarboxylates**

By *Manfred Schneider**, *Norbert Engel*, *Petra Hönicke*, *Gerd Heinemann*, and *Helmut Görisch*

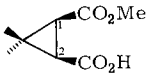
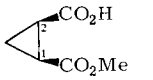
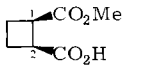
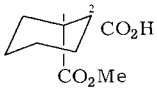
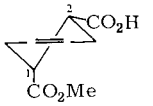
Enantioselective hydrolysis of the prochiral *cis*-1,2-diesters **1a–f** to the title compounds **2a–f** would afford versatile chiral building blocks for numerous applications, including natural products synthesis. Regardless of the resulting absolute configurations, the monoesters **2a–f** could serve as potential precursors for all possible enantiomers of these systems by selective group transformations, here exemplified by the selective conversion to the enantiomeric lactones **3** and *ent*-**3**, as well as by selective isomerizations to the *trans*-enantiomers **4** and *ent*-**4** and products thereof.



To make these reactions synthetically useful, **1a–f** should be conveniently accessible isomerically pure and in large amounts. While this is true for **1e**, **f**, the known stereoselective syntheses leading to **1a**, **c**, **d** from readily available starting materials were not satisfactory, and no method of synthesizing **1b** stereoselectively was known. We therefore developed a mild, general method for the concomitant isomerization and cyclization of *trans*-1,2-cycloalkanedicarboxylic acids using $(CF_3CO)_2O$; the *cis*-1,2-anhydrides obtained can be directly converted into **1a—f** using $MeOH/HC(OMe)_3$[2].

Enzymes can convert prochiral substrates into chiral products by enantiotopic group differentiation[1,3]. Porcine liver esterase not only shows high reaction selectivities, but also accepts a broad range of structurally different sub-

Table 1. Enzymatic hydrolysis of prochiral *meso*-diester **1** to chiral monoesters **2** [a, b].

Substrate	R	Product		pH	Reaction rate $t_{1/2}$ [h] (rel.)	$[\alpha]_D^{22}$	Enantiomer ratio (NMR)	Yield [%]
1a	CMe_2		(−)-(1*S*,2*R*)-**2a**	8	not measurable	—	—	—
				7	100 (1.5) [c]	−17.5 [e]	90 : 10	42
				8	50 (3) [c]	−17.0 [e]	85 : 15	50
1b	CH_2		(−)-(1*S*,2*R*)-**2b**	7	9 (17)	−15.0 [d]	>97 : 3	90
				8	3 (50)	−13.2 [d]	93 : 7	93
1c	$(CH_2)_2$		(+)-(1*R*,2*S*)-**2c**	7	2 (75)	+ 1.6 [d]	93 : 7	98
				8	1.5 (100)	+ 1.5 [e]	90 : 10	98
1d	$(CH_2)_3$		(+)-**2d** [h]	8	14 (10)	± 0 [d, e]	55 : 45	80
1e	$(CH_2)_4$		(+)-(1*S*,2*R*)-**2e**	7	14 (10)	+ 4.1 [e]	90 : 10	75
				8	1.5 (100)	+ 3.6 [e]	85 : 15	80
1f	$(CH_2CH{=})_2$		(+)-(1*S*,2*R*)-**2f**	7	5 (30)	+ 2.9 [d]	>97 : 3 [f]	94
				8	1.5 (100)	+ 2.8 [d]	>97 : 3 [f]	90

[a] All products were characterized spectroscopically [6]. [b] All experiments were run under standardized conditions (T = 26 °C, 10 mmol substrate, 40 mL 0.1 M phosphate buffer, 100 units = 1 mg porcine liver esterase/mmol substrate); [c] Experiments with 1000 units = 10 mg/mmol of **1a**; [d] (c 1, $CHCl_3$); [e] (c 1, MeOH); [f] Cf. [9]; [g] **2a** wast not numbered like a caronic acid but by analogy to **2b**, **c**, **e**, **f**; [h] Because of the low enantioselectivity of this reaction, the absolute configuration of (+)-**2d** has not yet been determined.

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strates[1a,3-5]. It therefore seemed an attractive reagent for the transformations **1**→**2**.

Hydrolysis of **1a—f** catalyzed by porcine liver esterase proceeded in 0.1 M phosphate buffer suspensions. The initial saponification was indicated by the decrease of pH, which was maintained at pH 7 or 8 by addition of 1 N NaOH. Only one ester group is saponified. After acidification, **2a—f** are recovered by extraction (Et_2O). Diastereomeric purities (to check for possible isomerizations) were determined by GC after reacidification (MeOH/$HC(OMe)_3$). Enantiomeric ratios were determined on the crude products by 250 MHz ^{1}H-NMR spectroscopy with (+)-(*R*)-α-methylbenzylamine, independent of, usually unreliable, rotational data of derivatives (Table 1).

The absolute configuration of **2a**[7] was known, that of **2b** was determined by selective base (NaH/dimethyl sulfoxide) isomerization to the known *trans*-enantiomer **4b**, and that of **2c** by conversion to the known[11b] lactones **3c**/*ent*-**3c**. The absolute configurations of **1e, f** were known from X-ray structure determinations[9].

The observed enantiomer ratios are quite high in most cases (somewhat higher at pH 7 than at pH 8, possibly due to some non-enzymatic hydrolysis) and can be further increased by recrystallization. The highest values were found for **2b** and **2f**, which were formed as enantiomerically pure compounds. The only exception was (+)-**2d**, which was formed in very low enantiomeric purity.

The absolute and relative reaction rates (Table 1) were determined under standardized conditions, although the amount of enzyme can be reduced from 100 (or 1000) to 10 units/mmol of substrate.

Whereas **1b—f** are transformed at synthetically useful rates (usually faster at pH 8 by a factor of 2 to 5), **1a** does not function as a substrate under these conditions[4]. Even at high enzyme concentrations the reaction **1a**→**2a** is very slow, making this process unsuitable synthetically despite the relatively high enantiomer ratio.

Because of the favorable enantiomer ratios and reaction rates, the formation of **2b, c, e, f** is of particular synthetic interest. The reactions were therefore scaled-up from the usual 10—50 mmol to 700—1000 mmol. For example, 100 g of optically pure (−)-**2b** can be obtained by this method in a single experiment.

Preliminary studies using esterase on CNBr-activated Sepharose (1.3 mg protein/mL gel; specific activity: 50% of the soluble enzyme) reveal that the enantiomeric purities obtained are identical for both enzyme preparations.

Experimental Procedure

(−)-**2b**: Porcine liver esterase (1000 units) is added to a vigorously stirred mixture of **1b** (15.8 g, 0.1 mol) and 100 mL phosphate buffer (0.1 M, pH 8). The start of the hydrolysis is indicated by a rapid decrease of the pH 8 value. pH 8 is maintained throughout the reaction ($t_{1/2} \approx 25$ h) by addition of 1 N NaOH. After addition of 100 mL (0.1 mol) NaOH the reaction stops. The cooled, stirred reaction mixture is acidified with 5 N HCl to pH 2 and extracted continously with Et_2O. The organic phase is dried, all solvents are removed, and the residue is treated with Et_2O (15 mL) and crystallized first at 0°C and subsequently for 2 d at −30°C. The colorless crystals of (−)-**2b**, 13.5 g (93%), m.p. = 82°C, $[\alpha]_D^{22}$ −13.2 (*c* 1.7, $CHCl_3$), are collected by filtration. Recrystallization from benzene (20 mL) yields 12 g of enantiomerically pure (−)-**2b**, $[\alpha]_D^{22}$ −15.3 (*c* 1, $CHCl_3$); 250 MHz ^{1}H-NMR (solvent $CDCl_3$): δ = 1.36 (m, 1H), 1.72 (m, 1H), 2.14 (m, 2H), 3.74 (s, 3H), 11.36 (bs, 1H).

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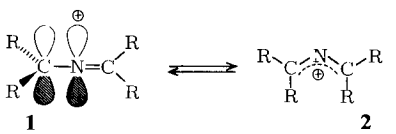
1a, 20315-30-4; **1b**, 826-34-6; **1c**, 2607-03-6; **1d**, 4841-91-2; **1e**, 1687-29-2; **1f**, 4841-84-3; (−)-**2a**, 81873-51-0; (+)-**2a**, 81873-49-6; (−)-**2b**, 88335-86-8; (+)-**2b**, 88335-87-9; (+)-**2c**, 88335-88-0; (−)-**2c**, 88335-89-1; **2d** (isomer 1), 88315-64-4; **2d** (isomer 2), 88335-90-4; (+)-**2e**, 88335-91-5; (−)-**2e**, 88335-92-6; (+)-**2f**, 88335-93-7; (−)-**2f**, 88335-94-8; **3c**, 88335-95-9; *ent*-**3c**, 75658-85-4; **4b**, 88335-97-1; *ent*-**4b**, 88335-96-0; esterase, 9013-79-0.

[1] a) F.-C. Huang, L. F. Hsu Lee, R. S. D. Mittal, P. R. Ravikumar, J. A. Chan, C. J. Sih, E. Caspi, C. R. Eck, *J. Am. Chem. Soc. 97* (1975) 4144; b) I. J. Jakovac, H. B. Goodbrand, K. P. Lok, J. B. Jones, *ibid. 104* (1982) 4659.
[2] M. Schneider, N. Engel, P. Hönicke, unpublished.
[3] For earlier work in this area see also: H. Kosmol, K. Kieslich, H. Gibian, *Justus Liebigs Ann. Chem. 711* (1968) 38.
[4] M. Schneider, N. Engel, H. Boensmann, *Angew. Chem. 96* (1984) 54; Angew. Chem. Int. Ed. Engl. 23 (1984) 66.
[5] M. Arita, K. Adachi, Y. Ito, H. Sawai, M. Ohno, *J. Am. Chem. Soc. 105* (1983) 4049.
[6] C. C. Shroff, W. S. Stewart, S. J. Uhm, J. W. Wheeler, *J. Org. Chem. 36* (1971) 3356.
[7] M.-J. De Vos, A. Krief, *J. Am. Chem. Soc. 104* (1982) 4282.
[8] The assignments for **2b, c** are, in our opinion, not unambiguous, and we are presently preparing derivatives of **2a—c** for X-ray structure analysis.
[9] We are grateful to Dr. *H.-J. Gais*, Darmstadt, for communicating his previous results with **1e, f**. H.-J. Gais, Habilitationsschrift, Technische Hochschule Darmstadt 1980, determined the absolute configurations of **1e, f** by X-ray structure analysis of the corresponding ephedrine salts. For applications in natural products synthesis: H.-J. Gais, K. L. Lukas, *Angew. Chem.*, in press.

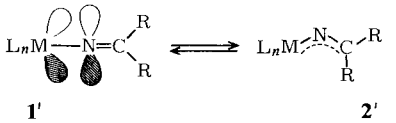
Hydrozirconation of Nitriles: Proof of a Linear Heteroallene Structure in (Benzylideneamido)zirconocene Chloride**

By *Gerhard Erker**, *Wolfgang Frömberg*, *Jerry L. Atwood*, and *William E. Hunter*

In general, dialkylideneammonium ions adopt a linear heteroallene structure (**1**, sp-hybridized nitrogen). Only exceptionally in cases of extreme stabilization of the carbenium ion center is a bent heteroallyl structure (**2**, *e.g.*, R = NR'_2) more favored[1]. Substitution of the carbenium carbon center by an isolobal, electron deficient metal fragment[2a], *i.e.* formal exchange of $CR_2^{\oplus}$ in **1** by the Cp_2ZrCl moiety[2b], leads to systems for which the structures **1'** and **2'**, analogous to **1** and **2**, respectively, are possible. How-



1 **2**



1' **2'**

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ever, the preferred ground-state structure of uncharged metal complexes can be determined experimentally much more easily than for the carbenium ion systems.

We obtained the *C*-substituted (methyleneamido)zirconocene chlorides **5a** and **5b** as moisture-sensitive, yellow solids in high yields by hydrozirconation of benzonitrile and acetonitrile, respectively[3]. In addition to the typical absorptions of the bent metallocene, an intense $-C=N$ stretching frequency is observed in the IR spectra of **5a** and **5b** (in toluene; $\nu = 1678$ and 1700 cm^{-1}, resp.). In Schiff's bases with $\geqslant C-N=CHR$ groups this band appears at slightly lower wave numbers[4]. The ^1H- and ^{13}C-NMR spectral data of the $-N=CHR$ moiety in the complex are very similar to those of many comparable organic systems[4]: ^1H, [^{13}C] ([D_6]benzene), **5a**: $\delta = 9.0$ [167.3 (d, $J = 168$ Hz)]; **5b**: $\delta = 8.3$ [167.5 (d, $J = 168$ Hz)]. It is noteworthy that a chemical differentiation of the cyclopentadienyl ligands on the zirconocene moiety, which would be expected for a metalla-allyl structure **2'**, cannot be detected by NMR spectroscopy in **5a**, even at low temperatures [Cp, ^1H [^{13}C] ([D_6]benzene): $\delta = 5.9$ [111.1]) or **5b** ($\delta = 5.8$ [110.7]).

X-ray structure analysis of **5a** (Fig. 1; crystals from toluene) confirms the chemical equivalence of the Cp ligands. The Cp(centr.),Zr,Cp'(centr.) plane is orientated orthogonally to the C(arom.),C1,H1 plane. The most striking feature of the molecular structure of **5a** is the almost linear Zr–N1–C1 moiety (170.5(5)°). The C=N bond distance (1.259(7) Å) is somewhat shorter than that of normal C=N (sp^2) double-bond systems. In contrast, the metal-nitrogen linkage is extremely short: at 2.013(5) Å in **5a** it is, to the best of our knowledge, the shortest Zr–N bond in a molecular zirconium compound known to date[5]. Despite this pronounced Zr–N1 interaction, the N1–Zr–Cl angle (101.1(2)°) and the Zr–Cl bond length (2.497(2) Å) are clearly within the normal order of magnitude[6].

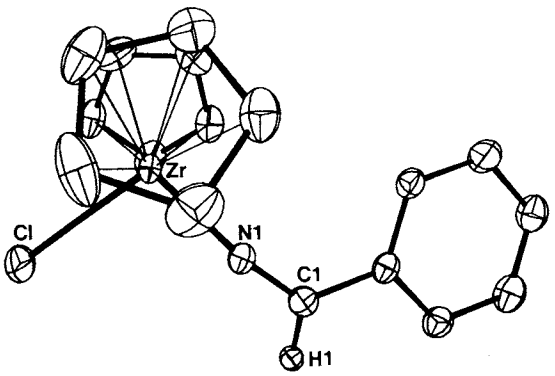
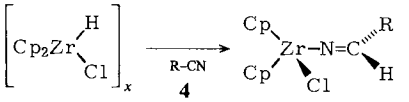


Fig. 1. Molecular structure of **5a** in the crystal. Space group $P2_1/c$; $a = 7.456(6)$, $b = 12.655(7)$, $c = 16.305(8)$ Å, $\beta = 94.09(6)°$, $V = 1534.6$ Å^3, $Z = 4$, 1695 observed reflexions, $R = 0.034$, $R_w = 0.041$. Details of the crystal structure investigation may be obtained from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen by quoting the depository number CSD 50559, the names of the authors, and the journal citation.

5a can therefore be considered as an organometallic compound with heteroallene structure of type **1'** with sp-hybridized nitrogen. In contrast to the trivalent carbenium ion center in **1**, the incorporation of the isolobal Cp_2ZrCl moiety with tetravalent zirconium could principally lead to stereoisomeric heteroallene systems. However, in the reaction of the nitriles **4** with **3** apparently only one isomer is formed in each case. In **5a**, Cl and H1 are arranged *cis* to the linear Zr–N1–Cl moiety; hydrozirconation usually proceeds with *cis*-stereochemistry[7].



3 **4** **5**

a, R = Ph; **b**, R = Me

The similarity between the structural chemistry of the positively charged organic system **1** and that of the electrically neutral organometallic compound **5** allows us to hope that other examples of "cation chemistry without charges" will be found in the future. Presently, we are investigating whether the resonance interaction between electronically unsaturated, bent, metallocene moieties and organic π systems gives rise to compounds which show reactions similar to resonance stabilized carbocations.

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3, 37342-97-5; **4a**, 100-47-0; **4b**, 75-05-8; **5a**, 61993-60-0; **5b**, 62053-83-2.

[1] E.-U. Würthwein, *Angew. Chem. 93* (1981) 110; *Angew. Chem. Int. Ed. Engl. 20* (1981) 99; *ibid. 95* (1983) 247; *22* (1983) 252; *Angew. Chem. Suppl. 1983*, 264; see also A. Schmidpeter, S. Lochschmidt, A. Willhalm, *Angew. Chem. 95* (1983) 561; *Angew. Chem. Int. Ed. Engl. 22* (1983) 545; *Angew. Chem. Suppl. 1983*, 710.

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The Scope of Radical CC-Coupling by the "Tin Method"**

By *Bernd Giese**, *Juan Antonio González-Gómez*, and *Tom Witzel*

Alkyl halides undergo CC-coupling on reaction with tributyltin hydride in the presence of electron-deficient alkenes[1]. We have now found that when alkyl iodides are employed in the reaction, the tin salts are necessary only as catalysts; moreover, we have also succeeded in carrying out the reaction with alcohols instead of with halides.

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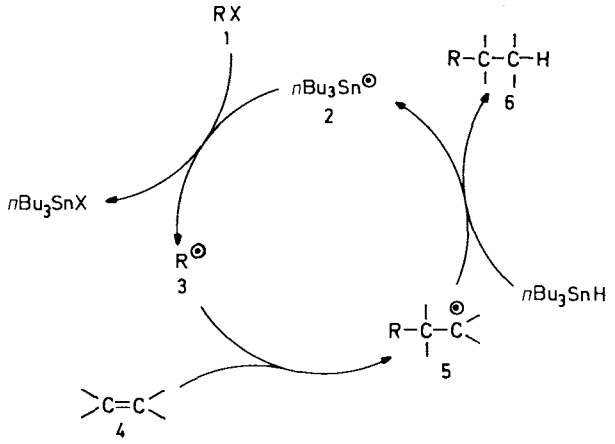
With **1** and **4** as educts, a radical chain reaction leads, via the intermediary radicals **2**, **3** and **5**, to formation of the products **6** (Scheme 1).



Scheme 1.

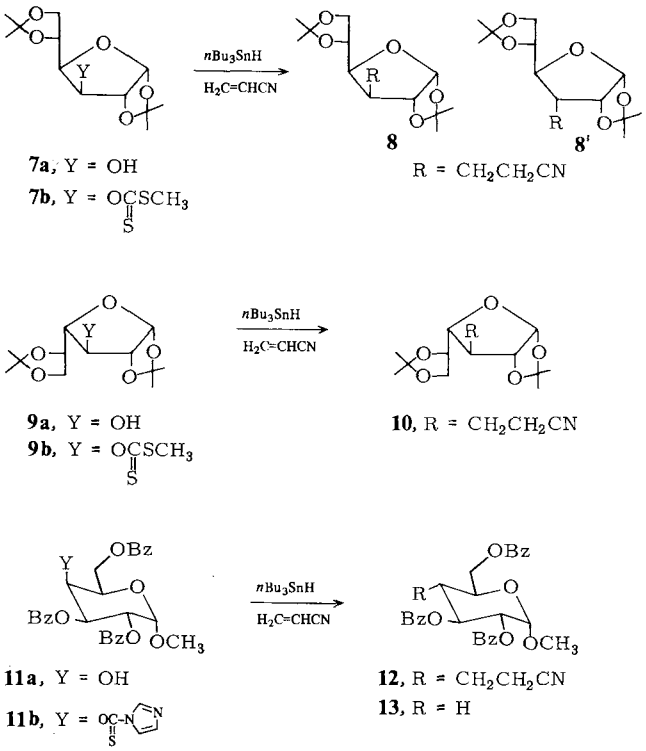
In the case of alkyl iodides the reactions could be carried out with substoichiometric amounts of organotin compounds because the butyltin hydride could be regenerated in situ from the tin halide with $NaBH_4$[2]. Thus, the photochemically initiated reaction of the alkyl iodides **1** (X = I) in ethanol at 25 °C with 0.2 molar equivalents of *n*-Bu_3SnCl and 1.3 molar equivalents of $NaBH_4$ in the presence of the alkenes **4** afforded the products **6** in yields of over 80% (Table 1).

Table 1. Yields of coupling products **6** in the reaction of alkyl iodides and thiocarbonyl compounds **1** (X = I, $OC(S)SCH_3$) with alkenes **4**.

RX	Alkene	Yield of **6** [%] [b]
n-$C_6H_{13}I$	H_2C=CHCN	80
t-C_4H_9I	H_2C=CHCN	87
cyclo-$C_6H_{11}I$	H_2C=CHCN	95
cyclo-$C_6H_{11}I$	H_2C=$CHCOCH_3$	85
cyclo-$C_6H_{11}I$	H_2C=$CHCO_2CH_3$	85
cyclo-$C_6H_{11}I$	H_2C=CHC_6H_5	83
cyclo-$C_6H_{11}I$	H_2C=CCl_2	87
cyclo-$C_6H_{11}I$	H_2C=$C(CH_3)CN$	91
cyclo-$C_6H_{11}I$	CH_3CH=CHCN [a]	86
cyclo-$C_6H_{11}OC(S)SCH_3$	H_2C=CHCN	63
cyclo-$C_6H_{11}OC(S)SCH_3$	H_2C=$CHCO_2CH_3$	50
cyclo-$C_6H_{11}OC(S)SCH_3$	H_2C=$C(CH_3)CN$	45
cyclo-$C_6H_{11}OC(S)SCH_3$	CH_3CH=CHCN [a]	40
7b	H_2C=CHCN	40 (75)
9b	H_2C=CHCN	35 (50)
11b	H_2C=CHCN	30

[a] 45 : 55 *cis* : *trans* mixture. [b] Gas-chromatographically determined yields in parenthesis.

This CC-coupling reaction could also be extended to thioacylated alcohols, analogously to the reduction method of *Barton* et al.[3]. Because of the photolability of the thiocarbonyl compounds, the syntheses were carried out in boiling toluene with azobis(isobutyronitrile) (AIBN) as initiator (Table 1). The versatility of this synthetic method is strikingly revealed on extending its application to carbohydrates: At 110 °C 1,2 : 5,6-di-*O*-isopropylidene-α-D-glucofuranose **7a**, afforded, via intermediary **7b**, the CC-coupling products **8** and **8′** (73 : 27)[4]; in contrast, the 1,2 : 5,6-di-*O*-isopropylidene-α-D-galactofuranose **9a** reacts diastereoselectively to give **10** (via **9b**). Accordingly, acrylonitrile preferably attacks the bicyclic radicals formed from **7b** and **9b** from the *exo*-side. This diastereoselectivity corresponds to the stereoselectivity of the deuteration with tributyltin deuteride[5].



The reaction of the thiourethane **11b** yielded the 4-(2-cyanoethyl)-**4**-deoxyglucopyranoside **12** as the product of CC-coupling. Other than in the unselective deuteration[6], here the equatorial substituents on C-3 and C-5 force an equatorial attack of acrylonitrile at C-4.

Besides the C-branched carbohydrates, about 10% of the corresponding deoxysugars are formed by reduction of the xanthates **7b** and **9b**. In contrast, in the case of **11b** the amount of CC-coupling and reduction, to give respectively **12** and **13**, was about the same.

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7b, 16667-96-2; **8**, 88336-56-5; **8′**, 88326-28-7; **9b**, 64481-59-0; **10**, 88326-26-5; **11b**, 88326-27-6; **12**, 88326-25-4; $H_3C(CH_2)_7CN$, 2243-27-8; $H_3CC(CH_3)_2CH_2CH_2CN$, 15673-05-9; *c*-$C_6H_{11}CH_2CH_2CN$, 41010-09-7; *c*-$C_6H_{11}CH_2CH_2COCH_3$, 2316-85-0; *c*-$C_6H_{11}CH_2CH_2CO_2CH_3$, 20681-51-0; *c*-$C_6H_{11}CH_2CH_2C_6H_5$, 1603-61-8; *c*-$C_6H_{11}CH_2CHCl_2$, 5173-61-5; *c*-$C_6H_{11}CH_2CH(CH_3)CN$, 64198-19-2; *c*-$C_6H_{11}CH(CH_3)CH_2CN$, 64198-20-5; H_2C=CHCN, 107-13-1; H_2C=$CHCOCH_3$, 78-94-4; H_2C=$CHCO_2CH_3$, 96-33-3; H_2C=CHC_6H_5, 100-42-5; H_2C=CCl_2, 75-35-4; H_2C=$C(CH_3)CN$, 126-98-7; *cis*-CH_3CH=CHCN, 1190-76-7; *trans*-CH_3CH=CHCN, 627-26-9; *n*-$C_6H_{13}I$, 638-45-9; *t*-C_4H_9I, 558-17-8; *c*-$C_6H_{11}I$, 626-62-0; *c*-$C_6H_{11}OC(S)SCH_3$, 41320-40-5; tributyltin hydride, 688-73-3.

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The Allyl Group as Mildly and Selectively Removable Carboxy-Protecting Group for the Synthesis of Labile *O*-Glycopeptides**

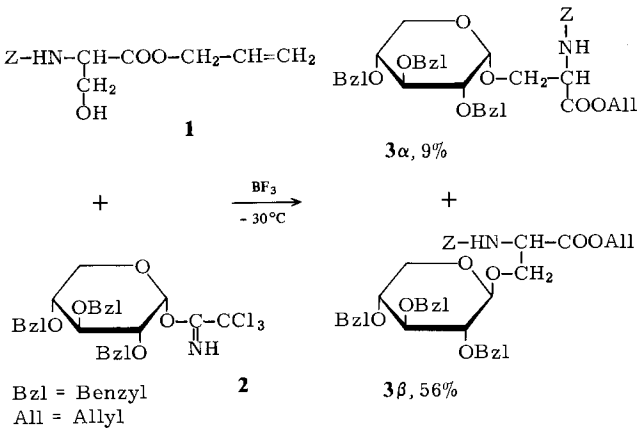
By *Horst Kunz** and *Herbert Waldmann*

Glycoproteins with a *O*-glycosidic bond between serine or threonine and the carbohydrate side chains fulfill important biological functions as membrane, serum, and connective tissue components. The synthesis of typical sections from such molecules is rendered difficult by the fact that the glycosyl-serine and -threonine bonds are both acid-labile as well as base-labile[1].

Selective carboxyl-deblocking and lengthening of the *C*-terminal chain can be achieved in glycosyl-serine derivatives by reductive elimination of the 2-haloethyl esters with zinc[2]. However, loss of material occurs by adsorption on the zinc salts.

We recently found that the allyl group can be used in peptide syntheses as a carboxy-protecting group which can be selectively removed in the presence of the benzyloxycarbonyl (Z) and the *tert*-butoxycarbonyl (Boc) groups under mild neutral conditions. The isomerization of the allyl moiety with tris(triphenylphosphane)rhodium(I) chloride[3] in ethanol/water at 70°C used in this reaction can also be used for liberation of the carboxy function in *N*-glycosylasparagine derivatives[4]. Herein we describe the extension of this method to the synthesis of labile *O*-glycopeptides and, therewith, an even gentler method for the cleavage of allyl esters.

The Z-serine allyl ester **1**, which is obtained by reaction of Z-serine with allyl bromide in 6% aqueous sodium hydrogen carbonate solution/dichloromethane in the presence of methyltrioctylammonium chloride, is first glycosylated with 2,3,4-tri-*O*-benzylxylopyranose according to the trichloroacetimidate method[5].



Unfortunately, the reaction does not proceed with the expected high β-selectivity[5]. The pure β-xylosylserine derivative **3β** can only be obtained by column chromatographic separation on silica gel. It shows a C-1 signal at $\delta = 104.7$ with $J(^{13}C\text{-}H) = 166.2$ Hz ([D$_6$]acetone) in the ^{13}C-NMR spectrum. The C-1 signal of the α-anomer **3α** appears at $\delta = 98.7$ (CD_3OD). Elemental analyses and ^1H-NMR spectra are also consistent with the structures **3α** and **3β**.

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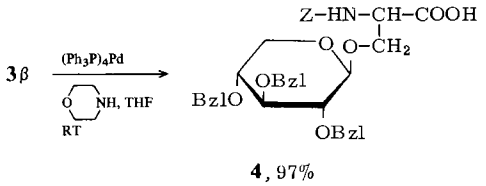
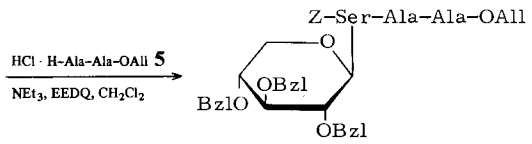
In order not to rupture the very labile *O*-glcoside bond in the glycosylserine derivative **3β**, we searched for an even milder method than the rhodium-catalyzed isomerization for cleavage of the allyl ester, and found this in the palladium(0)-catalyzed allyl transfer which *Trost* et al.[6] have used on several occasions for the allylation of carbanions. On reaction with ca. 10 mol-% of tetrakis(triphenylphosphane)palladium(0) under argon in tetrahydrofuran (THF) at room temperature the allyl residue of **3β** is transferred to morpholine (tenfold excess) as acceptor nucleophile. The cleavage of the allyl ester is almost quantitative.



4, 97%

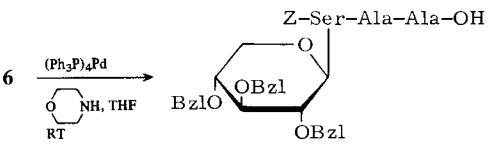


6, 87%

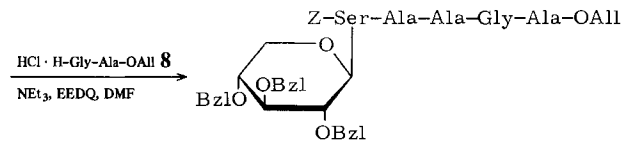
All the remaining functions of the glycosylserine derivative **3β** that are sensitive to acids, bases and to reduction are completely preserved. The carboxy-deblocked product **4** was identified by elemental analysis and by its spectra (^{13}C-NMR: $\delta = 104.9$, C-1; $J_{(^{13}C\text{-}H)} = 164$ Hz (CD_3OD).

For the synthesis of the glycopentapeptide **9**, whose mode of construction is based on data for the linkage region of an extracellular glycoprotein of the alga *Porphyridium crumtum*[7], the lengthening of the *C*-terminal chain of **4** is first undertaken by reaction with the dipeptide allyl ester **5**[4] in the presence of ethyl 2-ethoxy-1,2-dihydroquinone-1-carboxylate (EEDQ)[8]. The glycotripeptide allyl ester **6** is obtained in high yields. This reveals a further advantage of the small allyl group; its low lipophilicity promotes solubility, its sterically less-demanding size the condensation reactions.

It can also be demonstrated on the complex xylosyl-tripeptide ester **6** that the allyl moiety can be selectively and quantitatively removed by palladium(0) catalysis. Further enlargement of the product **7** (^{13}C-NMR: $\delta = 102.8$, C-1 ([D$_6$]dimethyl sulfoxide)) by the dipeptide unit **8** in dime-



7, 97%



9, 61%, $[\alpha]_D^{22} = -24.2$ ($c = 0.5$ CH_3OH)

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thylformamide (DMF) afforded the desired glycopentapeptide allyl ester **9**, whose structure was likewise confirmed by elemental analysis and spectroscopic data (^{13}C-NMR: $\delta = 102.9$, C-1, $J_{(^{13}C\text{-}H)} = 163$ Hz (dimethyl sulfoxide)).

The allyl group has thus proven to be a valuable achiral carboxy-protecting group even for difficult peptide and glycopeptide syntheses, and can be used in conjunction with *N*-terminal Z- and Boc-protecting groups. Also noteworthy is that the four glycopeptide allyl esters **3α**, **3β**, **6** and **9** are crystalline.

Procedure

N-Benzyloxycarbonyl-*O*-(2,3,4-tri-*O*-benzyl-β-D-xylopyranosyl)-L-serine **4**:

$(Ph_3P)_4Pd$ (0.15 g, 0.13 mmol) is added under argon at room temperature to a solution of **3β** (0.9 g, 1.32 mmol) in THF (10 mL) and the resulting mixture treated dropwise with 1.15 mL (13 mmol) morpholine. After 30 min the THF is distilled off in vacuo, the residue taken up in dichloromethane (50 mL), and the resulting solution extracted both with 2 N HCl (30 mL) and water, and dried over $MgSO_4$. After removal of the dichloromethane in vacuo, the residue is dissolved in ether, filtered, and the filtrate evaporated down. **4** remains as a colorless, amorphous solid; yield 0.82 g (97%), $[\alpha]_D^{22} = +18.3$ ($c = 1$, $CHCl_3$), ^{1}H-NMR: $\delta = 4.31$ (d, $J_{1,2} = 7.1$ Hz, 1H, H-1).

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1, 88295-41-4; **2**, 83441-63-8; **3α**, 88287-92-7; **3β**, 88287-93-8; **4**, 88287-94-9; **5**, 88287-95-0; **6**, 88287-96-1; **7**, 88287-97-2; **8**, 88287-98-3; **9**, 88287-99-4.

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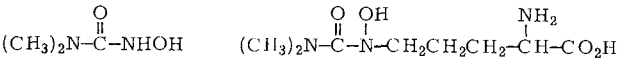
Unusual Components of the Toadstool *Lyophyllum connatum* (Agaricales)**

By *Burkhard Fugmann* and *Wolfgang Steglich**

The white fruiting bodies of *Lyophyllum connatum* are recommended by many field guides on mushrooms as edible and choice[1]. On spraying with aqueous $FeCl_3$ solution the mushroom shows an intense blue-violet color reaction—which prompted us to investigate the substances responsible.

After extraction of the fresh fungi[3] with methanol, evaporation of the solution to dryness and partition of the residue between water and ethyl acetate, the $FeCl_3$-positive compounds remained in the aqueous phase. By repeated gel-chromatography on various separating media, two of the compounds responsible for the color reaction could be obtained in pure form.

The substance present in smaller amounts (0.01–0.02%), m.p. 104–106 °C, proved to be identical with *N'*-hydroxy-*N,N*-dimethylurea **1**[4], a compound previously not found in nature.



1

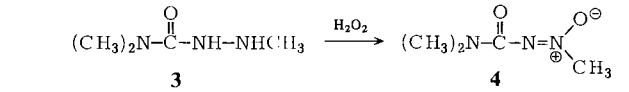
2

The main chromogen, connatin (m.p. 184–188 °C (dec.)) is present in the fresh fungus in amounts of 0.20–0.25%. From the spectroscopic data[5a] it follows that connatin has the formula of a N^{δ}-hydroxy-N^{ω},N^{ω}-dimethylcitrullin **2**. Since **2** affords a 2-trifluoromethyl-5(2*H*)-oxazolone[6] [^{1}H-NMR ($CDCl_3$): $\delta = 6.68$ (qt, $J = 4.6 + 2.3$ Hz, $CH{-}CF_3$)] on reaction with trifluoroacetic anhydride, the α-NH_2-group must be free. The terminal dimethylcarbamoyl group is recognizable in the EI-MS from the fragments *m/z* 104 ($C_3H_8N_2O_2$, 4%), 72 (C_3H_6NO, 94%) and 44 (C_2H_6N, 100%). Hydrolysis of **2** with 5% H_2SO_4 furnishes (*S*)-3-amino-1-hydroxy-2-piperidone[7], whereas with 6 N HCl (*S*)-N^{δ}-hydroxyornithine hydrochloride[8] is formed. The melting points and optical rotations of the two compounds agree with those quoted in the literature, thus proving the *S*-configuration for **2**.

N-Hydroxyamino acids have so far never been isolated from the fruiting bodies of higher fungi. Derivatives of N^{δ}-hydroxyornithine play an important role as sideramines and siderochromes in the transport of iron in microorganisms[9].

A further component, lyophyllin, m.p. 27–28 °C, can be isolated in 0.04% yield from the lipophilic fraction of the crude extract by twofold preparative thin-layer chromatography (silica gel, ethyl acetate).

From the spectroscopic data[5b] and the formation of *N,N*-dimethylurea upon hydrogenolysis, the structure of lyophyllin is *N,N*-dimethylazoxycarboxamide **4**; this has been confirmed by synthesis. Based on the procedure of *Mortarini* et al.[10], 1,4,4-trimethylsemicarbazide **3** was oxidized with 90% H_2O_2/maleic anhydride in dichloromethane (1 h 0 °C, 3 h 40 °C). The compound **4** obtained in 50% yield proved to be identical with the natural product. The stereochemistry of the compound awaits further investigation.



3 **4**

Lyophyllin is the first example of a alkylazoxycarboxamide. From cultures of *Calvatia* species (puffballs), *p*-cyanoazoxybenzoic acid (calvatic acid)[11] has been isolated, which has tumor-inhibiting properties. Simple aliphatic azoxy compounds and natural products of this structural type such as cycasin[12] or elaiomycin[13] are strong mutagens. Since *N*-hydroxyureas also interfere with DNA metabolism[14], a warning must be given about the consumption of this *Lyophyllum* species. After all, 1 kg of this toadstool contains 400 mg of lyophyllin **4** and more than 2 g of connatin **2**[15].

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CAS Registry numbers:
1, 52253-32-4; **2**, 88245-12-9; **3**, 62917-71-9; **4**, 88245-13-0.

[1] E. Michael, B. Hennig, H. Kreisel: *Handbuch für Pilzfreunde, Bd. 3*, VEB Gustav Fischer Verlag, Jena 1979, 3rd Edit., p. 380, and other reference works on fungi.

[2] The $FeSO_4$ mentioned in the literature is much less effective, since Fe^{II} must first be oxidized to Fe^{III} for complexation with **1** and **2**.

[3] Collected in October 1981 near the Karlburg, Karlstadt/Main (FRG).

[4] G. Zinner, G. Isensee, *Arch. Pharm. 307* (1974) 7.

[5] a) **2**: $[\alpha]_{589}^{22}$ +28.5 (c=1, H_2O); MW 219 (cryoscopic); empirical formula $C_8H_{17}N_3O_4$ (FAB-MS); ^{1}H-NMR (400 MHz, D_2O): δ=1.55 (m, 2H), 1.75 (m, 2H), 2.75 (s, 6H), 3.05 (t, J=7.5 Hz, 2H), 3.55 (t, J=5.5 Hz, 1H); ^{13}C-NMR (D_2O): δ=24.4 (tm, J=129+4 Hz, C-4), 30.2 (tm, 130+3, C-3), 40.0 (qq, 140+3.5, C-7), 55.0 (tt, 140+3, C-5), 57.0 (dt, 146+2, C-2), 168.4 (br. s, C-6), 177.0 (sdt, 4+4, C-1); we thank Prof. Dr. *H. Kelker* and Dr. *B. Bogdoll*, Hoechst AG, for the FAB-MS measurements; b) **4**: IR (CCl_4): 2979 (w), 1703 (vs), 1520 (s), 1430 (m), 1392 (s), 1349 (m), 1265 (m), 1155 (s), 550 cm^{-1} (m); ^{1}H-NMR ($CDCl_3$): δ=2.88, 3.02, 4.18 (each s, 9H); ^{13}C-NMR ($CDCl_3$): δ=35.4 (qq, J=140+3 Hz), 57.4 (q, J=144 Hz), 158.2 (br. s); MS: m/z 131 (M^+, $C_4H_9N_3O_2$, 5.7%), 72 (C_3H_6NO, 100).

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[8] Y. Isowa, T. Takashima, M. Ohmori, H. Kurita, M. Sato, K. Mori, *Bull. Chem. Soc. Jpn. 45* (1972) 1461.

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[13] R. Schoental: "Toxins Anim. Plant Origin" in A. De Vries, E. Kochva: *Proc. 2nd Int. Symp. Anim. Plant Toxins, Vol. 2*, Gordon and Breach 1972, p. 781; *Chem. Abstr. 82* (1975) 119915k.

[14] See *e.g.* R. J. Yu, E. J. van Scott, *J. Invest. Dermatol. 63* (1974) 279.

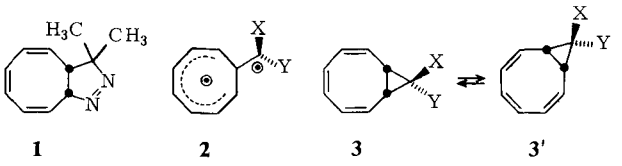
[15] The components **1**, **2** and **4** remain unchanged after boiling the fungi for 30 min.

Mechanism of the Cyclopropane "Walk" Rearrangement: Synthesis and Properties of the 2-Diazopropane Adduct of Cyclooctatetraene**

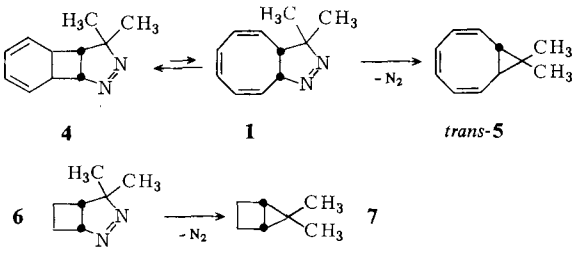
By *Frank-Gerrit Klärner** and *Volker Glock*

Whether the stereospecific cyclopropane "walk" rearrangement of the vinylogous systems bicyclo[2.1.0]pent-2-ene, bicyclo[4.1.0]hepta-2,4-diene (norcaradiene) and *cis*-bicyclo[6.1.0]nona-2,4,6-triene proceed concertedly or in two steps via diradicals cannot be unequivocally decided on the basis of the results of stereochemical and kinetic investigations alone[1]. An attempt was therefore made to generate the possible diradical intermediates via an independent route. We report here on the synthesis and thermolysis of **1**, which is a suitable precursor for a diradical of the type **2**, the potential intermediate of the "walk" rearrangement **3** → **3'**.

Cyclooctatetraene reacts with diazopropane differently than with diazomethane and diazoethane[2]; even at −15 °C the bicyclic dihydropyrazole **1** is primarily produced, which can be separated free of isomer from the tricyclic dihydropyrazole **4**, formed concomitantly as by-product, by reaction with *N*-phenylmaleimide and subsequent column chromatography (Fluorisil, ether-pentane (1:3), −20 °C; yield 7.6% referred to 2-diazopropane)[3]. Similarly, as in the case of other bicyclic cyclooctatriene derivatives[4], the valence isomerization **1** → **4** already occurs at room temperature (25 °C: $\tau_{1/2}$ = 89 min).



1 **2** **3** **3'**



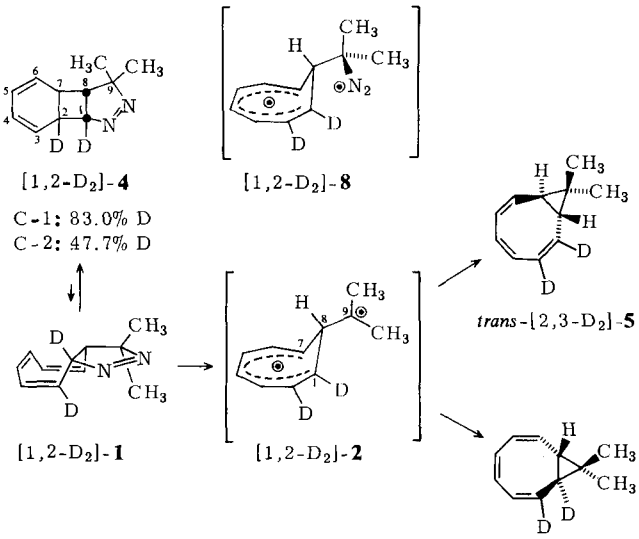
4 **1** *trans*-**5**

6 **7**

Scheme 1. $k_{1,4} = 6.3 \times 10^{11}$ exp [(−21.4 ± 0.4) kcal/RT]; $K = [\mathbf{4}]_\infty : [\mathbf{1}]_\infty \geq 100$; $k_{4,5} = 2.7 \times 10^{15}$ exp [(−34.3 ± 0.7) kcal/RT]; $k_{6,7} = 7.4 \times 10^{15}$ exp [(−39.8 ± 0.5) kcal/RT].

On heating the tricyclic dihydropyrazole **4** at 110 °C, up to 95% N_2-cleavage takes place to give the *trans*- and *cis*-9,9-dimethylbicyclo[6.1.0]nona-2,4,6-triene **5** in a ratio of 149 : 1[5] (gas chromatography). In addition, 5% cycloreversion to 3,3-dimethyl-3*H*-pyrazole[6] and benzene is also observed. The structure of the novel hydrocarbon *trans*-**5**[7] follows unambiguously from its spectral data[3]. From a comparison of the activation parameters of the reactions **4** → **5** and **6** → **7** given in Scheme 1, it emerges that the N_2-cleavage at 110 °C is 500 times more rapid than in the structurally related cyclobutene-diazopropane adduct **6**. This finding indicates that the N_2-cleavage does not occur from the tricycle **4** but from the valence isomeric bicycle **1**.

To gain further insight into the course of the reaction **4** → **5**, the thermal behavior of [1,2-D_2]-**4**, obtainable from



[1,2-D_2]-**4** [1,2-D_2]-**8**

C-1: 83.0% D
C-2: 47.7% D

[1,2-D_2]-**1** [1,2-D_2]-**2**

trans-[2,3-D_2]-**5**

trans-[1,2-D_2]-**5**

Scheme 2. Ratio of *trans*-[1,2-D_2]-**5** to *trans*-[2,3-D_2]-**5** at 110 °C: 50.8 : 49.2 (^{2}H-NMR), 51.9 : 48.1 (^{1}H-NMR); k_H/k_D = 1.19 ± 0.02.

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4 by base-induced H/D exchange in tetrahydrofuran (THF), was investigated ($KOt\text{-}C_4H_9$, D_2O-THF, room temperature, 16 h, yield 19%). The deuterium content quoted in Scheme 2 derives from the ^1H- and ^2H-NMR spectra. After partial thermolysis of [1,2-D_2]-**4** (110°C, 140 min, conversion: 50%), the content and position of the deuterium atoms in the recovered educt remain unchanged. According to the ^1H- and ^2H-NMR analyses, the main product consists of equal amounts of the regioisomers *trans*-[1,2-D_2]-**5** and *trans*-[2,3-D_2]-**5**.

The surprising formation of *trans*-**5** from the *cis*-configurated dihydropyrazole **4** can be explained as follows: After the valence-isomerization **4** → **1**, N_2-cleavage starts to take place from the *exo*-conformation of **1** shown in Scheme 2; this conformation of **1** is undoubtedly thermodynamically preferred over the corresponding *endo*-conformation. The structure of the likely diradical intermediates **8** and/or **2** resembles that of the homotropylium ion, and favors ring-closure to the *trans*-configurated bicyclo[6.1.0]nonatriene system. For formation of the *cis*-bicyclo[6.1.0]nonatriene, the intermediate must exist in the *endo*-conformation. Ring inversion obviously competes only to a very limited extent, if at all, with the ring-closure reaction. From the deuterium labeling experiment it can be concluded that the ring-closure between C-9 and C-1 proceeds at the same rate as that between C-9 and C-7. This finding can hardly be reconciled with the diazenyl diradical **8** as intermediate for the ring-closure. For the rear attack on the C atom bearing the diazenyl radical previously discussed in the literature, a preferred ring-closure between C-9 and C-7 would be expected. The experimental result, however, rather requires an intermediate having the symmetry properties of the N_2-free diradical **2**. The observation that the *cis*-configuration is preserved during the "walk" rearrangement in the *cis*-bicyclo[6.1.0]nonatriene system rules out the participation of a diradical intermediate of type **2** in this process.

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[1] Review: F.-G. Klärner, F. Adamsky, *Chem. Ber. 116* (1983) 299. F.-G. Klärner, *Top. Stereochem. 15*, in press.
[2] A. Calatroni, R. Gandolfi, *Heterocycles 14* (1980) 1115.
[3] ^1H-NMR (250 MHz, $CDCl_3$, TMS): **1** (−23°C): $\delta = 1.22$, 1.50 (s, $2CH_3$); 2.47 (d*, 8-H, $J_{1,8} = 7.6$ Hz); 5.52 (dd*, 1-H, $J_{1,2} = 6.3$ Hz); 5.64—5.79, 5.88—6.20 (m, 2-H to 7-H).—**4**: $\delta = 1.10$, 1.61 (s, $2CH_3$); 2.48 (m, 8-H, $J_{1,8} = 5.5$ Hz, $J_{2,8} = 1.0$ Hz, $J_{7,8} = 6.3$ Hz); 2.67 (m, 7-H, $J_{1,7} = 1.0$ Hz, $J_{2,7} = 9.3$ Hz, $J_{6,7} = 5.1$ Hz); 3.05 (m, 2-H, $J_{1,2} = 3.0$ Hz, $J_{2,3} = 3.0$ Hz); 5.16 (m, 1-H); 5.47 (dd*, 6-H, $J_{5,6} = 9.8$ Hz); 5.73 (m, 3-, 5-H); 5.86 (m, 4-H).—*trans*-**5** (C_6D_6): $\delta = 0.61$ (d*, 1-, 8-H, $J_{1,2} = J_{7,8} = 1.6$ Hz); 1.15 (s, $2CH_3$); 5.91—6.36 (m, 2-H to 7-H).—The signals marked with an asterisk are broadened by extensive coupling.
[4] Review: G. I. Frey, R. G. Saxton: *The Chemistry of Cyclo-octatetraene and its Derivatives*, Cambridge University Press, Cambridge (England) 1978, p. 40ff.
[5] a) *cis*-9,9-Dimethylbicyclo[6.1.0]nona-2,4,6-triene: S. W. Staley, T. J. Henry, *J. Am. Chem. Soc. 91* (1969) 1239; b) GC: 70 m glass capillary column, silicone oil OV 101, temperature 100°C, helium as carrier gas. *trans*-**5** is not entirely stable under the GC conditions; in some analyses it rearranges (up to *ca.* 3%) to a hydrocarbon which has the same retention time as *trans*-1,1-dimethyl-7,7a-dihydroindene.
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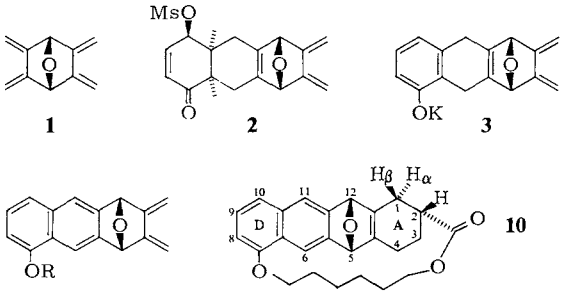
[7] The parent compound *trans*-bicyclo[6.1.0]nona-2,4,6-triene is formed, inter alia, in the photolysis of *cis*-bicyclo[6.1.0]nona-2,4,6-triene. W. Grimme, Habilitationsschrift, Universität Köln 1968; G. Masamune, P. M. Baker, K. Hojo, *Chem. Commun. 1969*, 1203.
[8] Review: P. S. Engel, *Chem. Rev. 80* (1980) 99. For the case of the diazenyl diradical **8** as an intermediate the rotation about the C8–C9 bond must be assumed to precede the ring-closure reaction. According to the observed stereoselectivity, conformational processes seem to compete with the ring-closure reaction to only a minor extent.

Macrocycles by Intramolecular Diels-Alder Reaction—Regioselective Synthesis of Anthracycline Precursors**

By *Joaquin Tamariz* and *Pierre Vogel**

The intramolecular Diels-Alder reaction is a powerful synthetic tool and has been applied widely[1]. Usually, the connective chain between diene and dienophile moieties consists of three to five atoms; if longer, the intramolecular reactivity and regio- and stereoselectivity decrease. It is therefore not surprising that this technique has not yet been widely used for the synthesis of medium-ring and macrocyclic compounds[2,3]. We report here an unusual regio- and stereoselective macrocyclic synthesis using an intramolecular Diels-Alder reaction. The method suggests a new approach to the synthesis of anthracycline precursors such as daunomycinone[4].



4, R = C_6H_5CO
5, R = H
6, R = $(CH_2)_3OH$
7, R = $(CH_2)_3OCOCH{=}CH_2$
8, R = $(CH_2)_6Br$
9, R = $(CH_2)_6OCOCH{=}CH_2$

Mesylate **2**, derived from **1**[5], furnished phenolate **3** upon treatment with KO*t*Bu. Reaction with benzoyl chloride, followed by oxidation with dichlorodicyanobenzoquinone gave **4** (95%, m.p. = 148–149°C). Inspection of simple molecular models indicates that an intramolecular Diels-Alder addition could be possible if, for example, acrylic acid were linked to naphthol **5** through a three-membered chain. Transesterification of **4** (K_2CO_3/CH_3OH) furnishes **5** (m.p. = 194–195°C, 98%). The corresponding naphthoate generated in tetrahydrofuran (THF) using NaH reacts with 3-bromopropanol (molar ratio 1 : 1, 70°C, 3 h) to give **6** (m.p. = 134–135°C, 96%). Esterification with acrylic acid yields 7 (51.5%). When dilute solutions ($< 8 \times 10^{-3}$ M) of **7** in xylene (with or without $ZnCl_2$ or $BF_3 \cdot Et_2O$) are heated to 140–240°C only polymerization was observed. The failure to observe macrocycle formation with **7** led us to choose a longer connecting chain between diene and dienophile.

The sodium naphthoate of **5**, generated using NaH in a mixture of THF and hexamethylphosphoric triamide (1 : 2) reacts with 1,6-dibromohexane (molar ratio 1 : 4, 0°C, 0.5 h) to yield bromide **8** (75%). Treatment with acrylic acid and 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) (molar ratio 2.2 : 2 : 1) in benzene (80°C, 2 h) afforded acrylate **9** as a

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colorless oil (63%), which polymerizes rapidly in the condensed state. When **9** was diluted in xylene (1.6×10^{-3} M) containing traces of hydroquinone and the solution heated to 170°C for 23 h, the macrocycle compound **10** was obtained as a homogeneous oil (58% after chromatography on silica gel) together with unreacted **9** and polymeric material. Characteristic data for compounds **7**–**10** are summarized in Table 1.

Table 1. Melting points and selected spectroscopic data of compounds **7**–**10**.

7: m.p. = 109–110°C; UV (CH_3CN): $\lambda = 300$ ($\varepsilon = 3600$), 252 (48100), 218 nm (45800); IR (KBr): $\nu = 1720$, 1595 cm^{-1}; ^{1}H-NMR ($CDCl_3$): $\delta = 8.16$, 7.67 (2s, 2H), 7.41 (d, $J = 8.2$ Hz, 1H), 7.37 (dd, $J = 7.4$, 8.2 Hz, 1H), 6.83 (dd, $J = 1.0$, 7.4 Hz, 1H), 6.44 (dd, $J = 1.6$, 17.6 Hz, 1H), 6.16 (dd, $J = 10.8$, 17.6 Hz, 1H), 5.85 (dd, $J = 1.6$, 10.8 Hz, 1H), 5.73, 5.70, 5.32, 5.26, 5.23 (5s, 5H), 4.5 (t, $J = 6.4$ Hz, 2H), 4.26 (t, $J = 6.0$ Hz, 2H), 2.32 (m, 2H). MS (70 eV): $m/z = 348$ (M^+, 56), 293 (13), 113 (100).

8: m.p. = 101–102°C; UV (CH_3CN): $\lambda = 302$ ($\varepsilon = 330$), 252 (48000), 218 (44900); IR (KBr): 2950, 1590, 1505 cm^{-1}. ^{1}H-NMR ($CDCl_3$): $\delta = 8.17$, 7.66 (2s, 2H), 7.39 (dd, $J = 2$, 8.0 Hz, 1H), 7.34 (t, $J = 8.0$ Hz, 1H), 6.82 (dd, $J = 2.0$, 8.0 Hz, 1H), 5.74, 5.71, 5.32, 5.26, 5.22 (5s, 5H), 4.13 (t, $J = 6.4$ Hz, 2H), 3.44 (t, $J = 6.6$ Hz, 2H), 1.93 (m, 4H), 1.59 (m, 4H); MS (70 eV): $m/z = 398$ (M^+, 20), 371 (4), 44 (100).

9: UV (CH_3CN): $\lambda = 302$ ($\varepsilon = 3400$), 252 (44700), 218 (42300); IR (film): $\nu = 2940$, 1725 cm^{-1}; ^{1}H-NMR ($CDCl_3$): $\delta = 8.15$, 7.65 (2s, 2H), 7.37 (dd, $J = 1.0$, 7.2 Hz, 1H), 7.33 (t, $J = 7.2$ Hz, 1H), 6.8 (dd, $J = 1.0$, 7.2 Hz, 1H), 6.40 (dd, $J = 1.3$, 17.2 Hz, 1H), 6.13 (dd, $J = 10.5$, 17.2 Hz, 1H), 5.81 (dd, $J = 13$, 10.5 Hz, 1H), 5.73, 5.69, 5.32, 5.26, 5.23 (5s, 1H), 5.21 (t, $J = 6.6$ Hz, 2H), 4.12 (t, $J = 6.6$ Hz, 2H), 1.95, 1.75, 1.62, 1.52 (4 quintet, $J = 6.6$ Hz, 4×2H); MS (70 eV): $m/z = 390$ (M^+, 75), 335 (25), 236 (100).

10: UV (EtOH): $\lambda = 334$ ($\varepsilon = 420$), 317 (700), 292 (sh, 41000), 280 (sh, 5600), 274 (sh, 5700), 252 (24600), 230 (20200); IR ($CHCl_3$): 3010, 2940, 1735, 1600 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 8.03 (s, 1H, 6-H), 7.51 (s, 1H, 11-H), 7.33 (dd, $J = 7.2$, 8.0 Hz, 1H, 9-H), 7.29 (dd, $J = 1.5$, 8.0 Hz, 1H, 10-H), 6.89 (dd, $J = 1.5$, 7.2 Hz, 1H, 8-H), 5.62 (m, 1H, 12-H), 5.60 (m, 1H, 5-H), 4.32 (t, $J = 5.5$ Hz, 2H, H_2C–OCO), 4.05 (ddd, $J = 3.4$, 5.2, 10.2 Hz), 3.73 (ddd, $J = 3.4$, 10.2, 11.2 Hz, 2H, H_2C–O), 2.58 (dm, $J = 18.0$ Hz, 1H, 1β-H), 2.27 (m, 2H, 2-H, 4β-H), 1.85–1.33 (m, 9H), 1.25 (m, 2H), 0.77 (dddd, $J = 4.0$, 6.0, 10.0, 18.0 Hz, 1H, 3α-H), cf. also text; MS (70 eV): $m/z = 390$ (M^+, 11), 234 (100); MS (CI, CH_4): 391 ($M^+ + H$).

The structure of **10** was determined using 360 MHz ^{1}H-NMR spectroscopy (cf. also Table 1). The distinction between the signals of the aromatic protons 6-H and 11-H is based on NOE measurements. Similarly, the signals of the bridgehead protons 5-H and 12-H was obtained using NOE measurements (proximity to 6-H and 11-H, respectively). A homoallylic ^5J coupling constant of 1.7 Hz was measured between 1β-H and 5-H. This is somewhat larger than expected (1–1.4 Hz) for cyclohexenes annelated to 7-oxanorbornenes[6] and suggests a blocked conformation of the A-ring with 1β-H in an axial position (Fig. 1). The coupling constants $^4J_{12\text{-H},1\beta\text{-H}} = 0.2$–$0.3$ Hz and $^5J_{4\beta\text{-H},12\text{-H}} = 0.2$–$0.3$ Hz were observed, confirming a blocked chair conformation in which 4β-H is equatorial. 2-H couples with 1β-H and 1α-H with relatively *small* vicinal coupling constants (3–4 Hz); 2-H also couples strongly with 3α-H (10 Hz) and weakly with 3β-H (<1 Hz). The measured coupling constants between 3α-H and 4β-H (6 or 4 Hz) and between 3α-H and 4α-H (4 or 6 Hz) are in agreement with structure **10** and the conformation depicted in Figure 1.

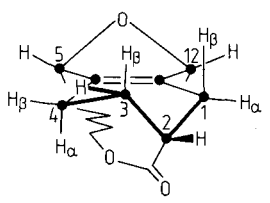

Fig. 1. Conformation of the "right part" of **10** (schematic).

Variation of the concentration of **9** ($1\text{–}4 \times 10^{-3}$ M) did not affect the yield of **10**, as expected for an intramolecular Diels-Alder addition. Inspection of molecular models suggests a preferred attack at the *endo* face, thus requiring the acrylic ester in **9** to adopt an orientation consistent with Alder's *endo* rule. Compound **10** can be viewed as an eighteen-membered ring *ansa*-lactone[7].

The transformation of tetraene **1** into **10** suggests a new approach to the total synthesis of anthracycline precursors involving control of the regiostereoselectivity of the substituents of ring A with respect to those of ring D[8]. Methods for generating **2** in optically pure form and for stereoselective transformation of **10** into daunomycinone[9] are being investigated.

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CAS Registry numbers:
1, 53011-99-7; **2**, 88336-07-6; **3**, 88315-90-6; **4**, 88315-91-7; **5**, 88315-92-8; **5**·Na, 88315-98-4; **6**, 88315-93-9; **7**, 88315-94-0; **8**, 88315-95-1; **9**, 88315-96-2; **10**, 88315-97-3; 3-bromopropanol, 627-18-9; acrylic acid, 79-10-7; 1,6-dibromohexane, 629-03-8.

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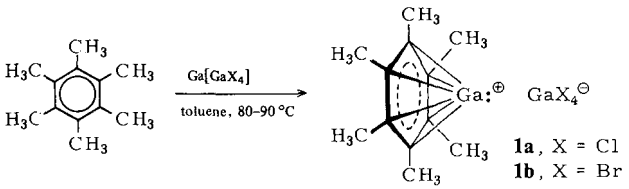
Preparation and Structure of (η^6-Hexamethylbenzene)gallium(I) Tetrabromogallate(III): π-Complex and *nido*-Cluster

By *Hubert Schmidbaur**, *Ulf Thewalt*, and *Theodore Zafiropoulos*

Over a hundred years ago, the discoverer of the element gallium[1] reported the astonishing observation that the preparations which he termed gallium(II) halides of empirical formula GaX_2 (X = Cl, Br) are freely soluble in anhydrous benzene and can be precipitated from solution with "crystal benzene"[2]. Whereas, on the one hand, the dihalides have been characterized in the meantime in the crystalline and molten states by different methods as $Ga^{I}Ga^{III}X_4$[3], and, on the other hand, their dioxane complexes had to be interpreted as compounds, $X_2Ga-GaX_2\cdot(C_4H_8O_2)_2$, with metal-metal bonds[4], the nature of the interaction between "$GaCl_2$" and "$GaBr_2$" and aromatic hydrocarbons remained unclear. It was certainly presumed by many authors that "π-complexes" could be involved[2], but experimental evidence for this remained elusive. The same applied to the benzene adduct of $Tl[AlCl_4]$[5].

Following the elucidation of the benzene-richest phase in the system $Ga[GaCl_4]$/benzene as a tetranuclear complex with two bis(η^6-benzene)gallium(I) moieties[6], we now report the first monoarene complex of gallium(I).

Suspensions of Ga_2Cl_2 or Ga_2Br_4 in anhydrous toluene rapidly become clear upon addition of excess hexamethylbenzene and heating to 80–90 °C; upon cooling the colorless reaction solution crystals of overall composition $Ga_2X_4\cdot C_6Me_6$ precipitate (**1a**, X = Cl, m.p. = 168 °C: **1b**, X = Br, m.p. = 146 °C).



No evidence for other products was found, which is significant in as far as both benzene and 1,3,5-trimethylbenzene form primary products with $(arene)_2Ga^{\oplus}$ structural units[6,7]. Furthermore, it is significant that the hexamethylbenzene added to the toluene is apparently preferred as a ligand. The ^1H- and ^{13}C-NMR spectra of solutions of **1a** in CD_2Cl_2 exhibit signals from the hexamethylbenzene ligand: $\delta(CH_3) = 7.90$, $\delta(CH_3) = 17.15$, $\delta(C) = 136.51$ (rel. TMS).

The X-ray structure analysis of **1b**[8] indicates that a polycoordinated network is present (Fig. 1), composed principally of $Me_6C_6Ga^{\oplus}$ cations and $GaBr_4^{\ominus}$ anions.

Whereas the Ga^{III} center (Ga1) exhibits only a slightly distorted tetrahedral environment of four bromine atoms (Br1 to Br4; cf. Fig. 1), the Ga^{I} center (Ga2) is bonded principally to the hydrocarbon, 2.552 Å vertically above

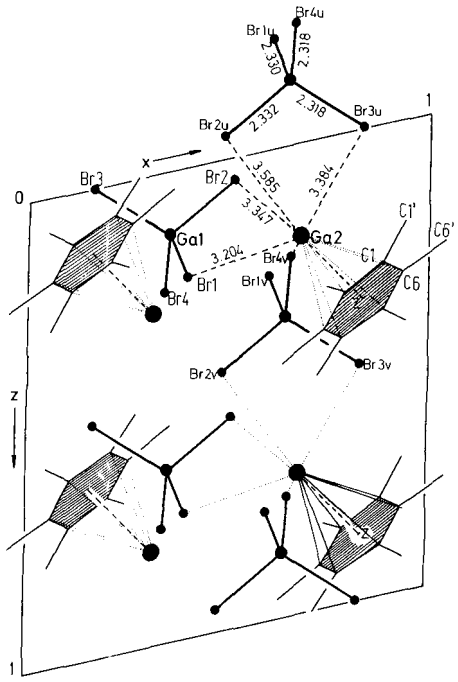


Fig. 1. Projection of the crystal structure of $Ga_2Br_4\cdot C_6(CH_3)_6$ **1b** along the crystallographic y-axis. To clarify matters, the contacts to the neighboring atoms are only shown for two of the Ga^{I} atoms (large circles, Ga2). Supplementary parameters: Ga2–Br4v 3.347, Ga2–C1 2.871, Ga2–C2 2.915, Ga2–C3 2.897, Ga2–C4 2.869, Ga2–C5 2.896, Ga2–C6 2.877. u and v signify the transformations $1-x, -y, -z$ and $1-x, -\frac{1}{2}+y, \frac{1}{2}-z$, respectively. Standard deviations for Ga–C and Ga–Br distances are 0.009 and 0.002 Å, respectively.

the centroid of the six-membered ring. The average Ga2–C distance is 2.888(18) Å. The other sites in the coordination sphere of Ga2 consist of five bromine atoms which originate from three different $GaBr_4$ tetrahedra (Fig. 1). Two of the "ligand tetrahedra" form chelates; one is only monodentate. The associated Ga–2Br distances vary over the range 3.204 to 3.585 Å. The overall coordination of Ga2 can be interpreted as distorted octahedral if the arene (formally its center Z) is assigned to one corner of an octahedron (Fig. 2). The distorsion principally arises because Ga2 is markedly displaced towards the arene.

The complexed hexamethylbenzene displays systematic deviations from planarity: C1 and C4 project out of the "ring plane" in the Ga2 direction; in contrast, C2, C3, and C5 are displaced in the opposite direction. The positions of the CH_3 groups express this pattern particularly clearly[9].

The model of π-complex formation and the cluster formalism both offer theoretical descriptions of the bonding of the arene Ga^{I}. In the qualitative MO scheme the former emphasizes the interaction between the filled bonding orbitals a_1 and e_1 of the arene (C_{6v}) and the empty symmetry-equivalent sp_z and p_x/p_y orbitals of Ga^{I}. The relationship with the known arene complexes of Sn^{II} is discernible from the isoelectronic relationship[10]. Within the framework of the cluster formalism, $Me_6C_6Ga^{\oplus}$ can be considered as the *nido*-form of a polyhedron closely related to the cyclopentadienylgermanium(II) and cyclopentadienyltin(II) cations, which are also well known[11].

Comparison with the $(C_6R_6)_2Ga^{\oplus}$ complexes[6] indicates that the metal-arene bond in **1a, b** is considerably stronger than in bis(benzene)gallium(I) and bis(mesitylene)gallium(I)[7], which have ring centroid-metal distances of 2.764/2.929 and 2.673/2.673 Å, respectively. Since the ar-

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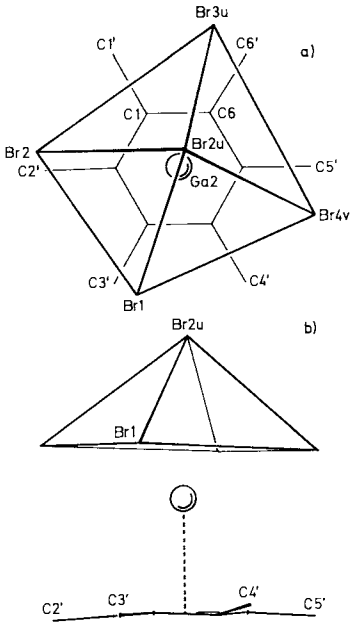

Fig. 2. Coordination sphere of an individual Ga' atom. a) Projection perpendicular to the best plane through the C_6 ring; b) side view of the same moiety.

ene ligand functions as a donor in each case, the shorter distance in **1a, b** can certainly be attributed to the inductive effect of the six methyl groups. The order of stability $C_6Me_6 > C_6H_3Me_3 > C_6H_5Me > C_6H_6$ is therefore not surprising. The C_6H_6 ligand is so loosely bound that it can be removed at room temperature under reduced pressure[6]. However, additional steric effects and symmetry phenomena may predominate over the inductive effect.

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CAS Registry numbers:
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[8] Crystal data: Monoclinic, $P2_1/c$; lattice constants (at $-40°C$): $a = 10.906(3)$, $b = 13.994(5)$, $c = 12.415(4)$ Å, $\beta = 103.90(2)°$; $Z = 4$; $Mo_{K\alpha}$ irradiation ($\lambda = 0.71069$ Å, 2448 independent reflections ($2\theta_{max} = 48°$) with $F_0 \geq 3.92\,\sigma(F_0)$); empirical absorption correction (ψ-scan, $\mu = 113.6$ cm^{-1}). Structure solved using Patterson method; refined with anisotropic temperature factors (without H atoms): $R = 0.054$, $R_w = 0.061$. Further details of the crystal structure investigation can be obtained from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen, by quoting the depository number CSD 50556, the names of the authors and the journal citation.

[9] Equation of the best plane through C1 to C6 (relative to the *abc* basis): $5.408x + 5.089y + 8.024z - 7.610 = 0$. Deviations of the atoms from it: C1 −0.018, C2 0.016, C3 0.005, C4 −0.024, C5 0.022, C6 −0.001, C1' −0.041, C2' 0.123, C3' 0.067, C4' −0.127, C5' 0.138, C6' 0.016, Ga2 −2.522 Å. Angle between the normal to the plane and the vector from Ga2 to the ring centroid: 0.5°.

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Hydrolysis Products of the Monomeric Amine Complex $(C_6H_{15}N_3)FeCl_3$: The Structure of the Octameric Iron(III) Cation of $\{[(C_6H_{15}N_3)_6Fe_8(\mu_3\text{-}O)_2(\mu_2\text{-}OH)_{12}]Br_7(H_2O)\}Br \cdot 8H_2O$

By *Karl Wieghardt**, *Klaus Pohl*, *Ibrahim Jibril*, and *Gottfried Huttner*

Dedicated to Professor Ernst Otto Fischer on the occasion of his 65th birthday

The chemistry of Fe^{III} compounds in aqueous solution is underscored by their tendency to undergo hydrolysis and by the condensation of $Fe(OH_2)_6^{3\oplus}$. Hydroxo- and oxo-bridged oligomers are formed before the precipitation of sparingly soluble $Fe_2O_3 \cdot n\,H_2O$[1]. Nevertheless, the characterization of oligomers containing more than three Fe^{III} centers has so far never been reported. Hydrolysis of the monomeric complex (tacn)$FeCl_3$ **1** (tacn = 1,4,7-triazacyclononane) in the presence of acetate leads to formation of the binuclear complex $[(tacn)_2Fe_2(\mu_2\text{-}O)(\mu_2\text{-}CH_3CO_2)_2]^{2\oplus}$ **2**[2]; in the absence of potential ligands such as acetate the dimeric, green $[(tacn)_2Fe_2(H_2O)_2(\mu_2\text{-}O)_2]^{2\oplus}$ **3** is formed at pH 9, and it can be isolated as the iodide or as the PF_6^- or ClO_4^-salt[3a]. Hydrolysis of **1** at 20°C (pH 9) in the presence of bromide leads within 24 h to precipitation of brown crystals of the compound $[(tacn)_6Fe_8(\mu_3\text{-}O)_2(\mu_2\text{-}OH)_{12}]Br_8 \cdot 9\,H_2O$ **4**[3b].

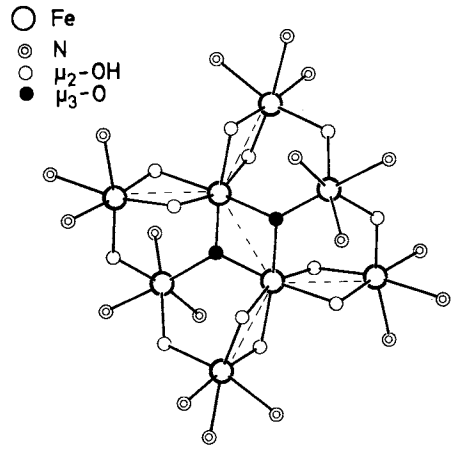

Fig. 1. Skeleton of the octameric cation of **4** (only Fe, O, and N atoms are shown). Mean distances: Fe–N 2.17 Å, Fe–OH 1.98 Å, Fe–(μ_3-O) 1.93 Å. Short Fe···Fe distances (broken lines) 3.05 Å.

The X-ray structure analysis of **4** shows that an octameric Fe^{III} cation is formed[4], in which only six of the eight Fe^{III} atoms are bonded to an amine ligand (FeN_3O_3); two central Fe^{III} atoms are each surrounded by a distorted oc-

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tahedral array of six O-atoms. The iron ions are coupled together by twelve μ_2-hydroxo bridges and by two μ_3-oxo bridges (Fig. 1). The cyclic amine ligands form a hydrophobic "surface" of the complex cation (Fig. 2). There are five relatively short Fe···Fe distances (≈305 pm), which arise from edge-to-edge coupling of octahedra via oxo- or hydroxo-bridges, and eight longer ones (≈345 pm). The cation has idealized C_i-symmetry.

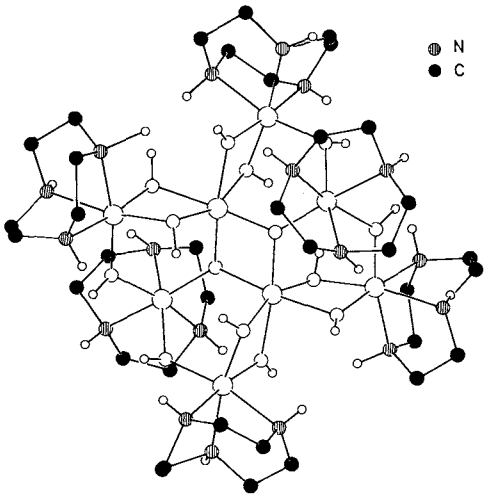

Fig. 2. The complex cation **4** with the 1,4,7-triazacyclononane ligands.

The high ionic charge 8+ in the solid state is almost compensated by seven associated $Br^{\ominus}$ ions. These are bound to the cation by electrostatic forces and hydrogen bonding (via NH-anions and OH-groups (Fig. 3); six of them are arranged pairwise in an idealized centrosymmetric array. Only the pendant to Br7 is missing. This position is occupied by a H_2O-molecule, whereby the C_i symmetry of the cation is destroyed (consequently the space group is also acentric P1 and not $P\bar{1}$). That is, the cation in **4** can be regarded as a bromide ion-carrier complex:

$$\{[(tacn)_6Fe_8(\mu_3\text{-}O)_2(\mu_2\text{-}OH)_{12}]Br_7 \cdot H_2O\}^{\oplus}$$

The counterion $Br^{\ominus}$ occupies an idealized inversion center (1/2, 1/2, 1/2) and binds eight H_2O molecules, four of which exhibit O—H···Br interactions (Fig. 3); the remaining four H_2O molecules are coupled with the directly coordinated H_2O molecules via O···H—O bonds (O···O distance 270—280 pm).

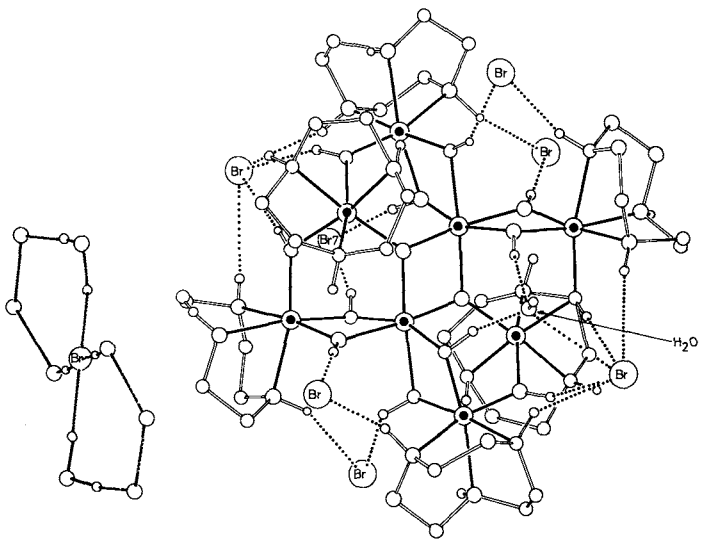

Fig. 3. The structure of $\{[(tacn)_6Fe_8(\mu_3\text{-}O)_2(\mu_2\text{-}OH)_{12}]Br_7 \cdot H_2O\}^{\oplus}$ and $[Br \cdot 8\,H_2O]^{\ominus}$.

The cation-anion lattice of

$$\{[(tacn)_6Fe_8(\mu_3\text{-}O)_2(\mu_2\text{-}OH)_{12}]Br_7 \cdot H_2O\}^{\oplus}[Br \cdot 8\,H_2O]^{\ominus}$$

is of type AB; it corresponds to a distorted NaCl structure.

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1, 86823-88-3; **3**·2$I^{\ominus}$, 88271-92-5; **3**·2$PF_6^{\ominus}$, 88271-94-7; **3**·2$ClO_4^{\ominus}$, 88271-96-9; **4**, 88271-95-8.

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[3] Experimental: a) $[(tacn)_2Fe_2(\mu_2\text{-}O)(OH_2)_2]I_2 \cdot H_2O$: 0.25 g (tacn)$FeCl_3$ [2] was dissolved in 20 mL H_2O and 2 mL pyridine at 25°C. After 15 min 1 g of NaI (or KPF_6, $NaClO_4$) was added to the solution. A green precipitate (0.2 g) of the salt containing the cation separated out [μ_{eff}(103 K) = 2.2, μ_{eff}(293 K) = 2.6 μ_B per Fe center].—b) $[(tacn)_6Fe_8(\mu_3\text{-}O)_2(\mu_2\text{-}OH)_{12}]Br_8 \cdot 9\,H_2O$: An analogously prepared green solution was treated with 5 g NaBr and allowed to stand for 24 h at 20°C. After 12 h the solution turned brown, and over the following 12 h brown crystals separated out (0.15 g). Between 103 and 193 K the magnetic amoment of **4** obeys the Curie-Weiss law ($\mu_{eff} = 3.72\ \mu_B$; $\vartheta = 59.9$ K).—All the salts gave correct elemental analyses.

[4] Crystal structure analysis of **4**: $C_{36}H_{120}O_{23}N_{18}Fe_8Br_8$; P1, $Z=1$; $a = 10.522(7)$, $b = 14.05(1)$, $c = 15.00(1)$ Å, $\alpha = 89.90(6)$, $\beta = 109.65(5)$, $\gamma = 109.27(6)°$, $V = 1956$ Å^3 ($T = -30$°C); $\rho_{calc} = 1.92$ g/cm^3; $Mo_{K\alpha}$, $\lambda = 0.71069$ Å, scan $2.0° < \omega < 29.3°$, $2° < 2\vartheta < 42°$; 4213 reflections (3996 with $I > 2\sigma(I)$); direct methods (SHELX-TL revision 3.0). H atoms of NH- and OH-groups as well as some of those of the H_2O molecules were observed, those of the CH_2-groups ignored. For 450 parameters $R_1 = 0.047$, $R_2 = 0.051$. Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen on quoting the depository number CSD 50630, the names of the authors, and full citation of the journal.

Stable Olefin Complexes of Pt(II) Containing Trichlorostannate(II) Ligands: Structure of $[Ph_4As][Pt(SnCl_3)_3(1,5\text{-cod})]$**

By *Alberto Albinati, Paul S. Pregosin**, and *Heinz Rüegger*

Olefin complexes of platinum(II) containing the trichlorostannato ligand have been postulated as intermediates in catalytic hydrogenations and hydroformylations[1]; however, these compounds have not been isolated. As part of our program[2], we prepared the stable anionic complexes of type **1** starting from Zeise's salt and analogous Pt^{II} compounds[7].

$$[PtCl_3(olefin)]^{\ominus} + SnCl_2 \xrightarrow{CH_2Cl_2} cis\text{-}[PtCl_2(SnCl_3)(olefin)]^{\ominus}$$

1a, olefin = C_2H_4
1b, olefin = CH_2=CHPh
1c, olefin = *cyclo*-C_8H_{14}
1d, olefin = CH_2=$CHCH_2OH$

Complexes **1a—1d** can readily be characterized using ^{119}Sn-, ^{195}Pt-, and ^{13}C-NMR spectroscopy. Their molecular

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geometries were deduced from the values of $^1J(^{195}Pt,^{119}Sn)$, which are dependent on the nature of the trans ligand[3]. **1a** is isolable as its PPN salt $(PPN=(Ph_3P)_2N^{\oplus})$[3] and is interesting in that its trans isomer may be an intermediate in the $SnCl_2$-catalyzed synthesis of Zeise's salt[4].

Addition of more than one equivalent of $SnCl_2$ to **1a** promotes loss of C_2H_4; however, starting from the olefin complex $[PtCl_2(diolefin)]$, the five-coordinate tris(trichlorostannato)platinum(II) complexes **2** and **3** may be isolated in good yield.

$$[PtCl_2(diolefin)] + 2\,SnCl_2 + SnCl_3^{\ominus} \longrightarrow [Pt(SnCl_3)_3(diolefin)]^{\ominus}$$

2, diolefin = 1,5-cyclooctadiene
3, diolefin = norbornadiene

The structure of the anion **2**[5] (see Fig. 1) may be thought of as a distorted square pyramid in which Sn3 occupies the axial position. To our knowledge **2** is the first example of a platinum-tin complex exhibiting a square pyramidal geometry.

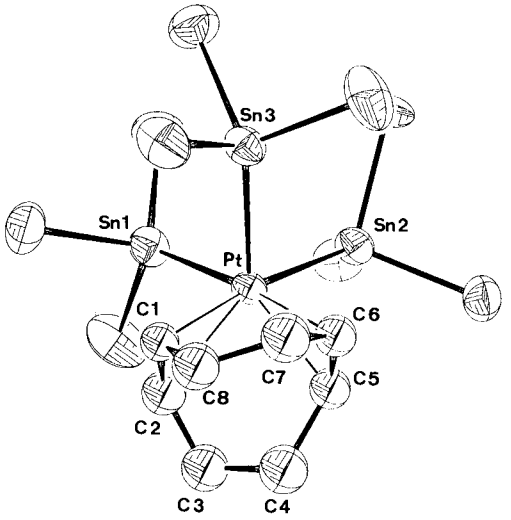

Fig. 1. ORTEP diagram of the complex anion **2** in the crystal of the salt $[Ph_4As][Pt(SnCl_3)_3(1,5\text{-cod})]$. Selected bond lengths [Å] and bond angles [°]: Pt–Sn1 2.568(2), Pt–Sn2 2.546(2), Pt–Sn3 2.643(2), Pt–C1 2.23(2), Pt–C2 2.23(2), Pt–C5 2.27(2), Pt–C6 2.23(2), Sn–Cl (average) 2.355(6), C–C (average) 1.48(3); Sn1–Pt–Sn2 85.90(5), Sn1–Pt–Sn3 94.83(5), Sn2–Pt–Sn3 93.80(5).

All three Pt–Sn distances are relatively long; the value for Pt–Sn3 (2.643 Å) is more than 0.04 Å longer than that observed in either $[Pt(SnCl_3)_5]^{3\ominus}$[6a] or $[Pt(SnCl_3)_3(AsMe_3)_2]^{\ominus}$[6b] and is 0.287 Å longer than the Pt–Sn distance in *cis*-$[PtCl_2(SnCl_3)_2]^{2\ominus}$[6c].

This relatively long Pt–Sn3 distance is compatible with the observation that this complex exhibits a dynamic structure on the NMR scale in solution.

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[2] M. Kretschmer, P. S. Pregosin, M. Garralda, *J. Organomet. Chem. 244* (1983) 175; M. Kretschmer, P. S. Pregosin, H. Rüegger, *J. Organomet. Chem. 241* (1983) 87; K. H. A. Ostoja Starzewski, P. S. Pregosin, H. Rüegger, *Helv. Chim. Acta 65* (1982) 785 and references cited therein.

[3] $^1J(^{195}Pt,^{119}Sn)$ is normally > 27000 Hz for $SnCl_3^{\ominus}$ *trans* to $Cl^{\ominus}$. PPN-**1a** (in $CDCl_3$, 223 K): ^{119}Sn-NMR: $\delta = -427$, $^1J(^{195}Pt,^{119}Sn) = 27950$ Hz; ^{195}Pt-NMR: $\delta = -3764$ (rel. Na_2PtCl_6); ^{13}C-NMR: $\delta = 66.2$, $^1J(^{195}Pt,^{13}C) = 171$ Hz.

[4] R. Pietropalo, M. Graziani, U. Belluco, *Inorg. Chem. 8* (1969) 1506.

[5] The Ph_4As salt of **2** is monoclinic; space group $P2_1/n$; $a = 15.445(2)$, $b = 9.807(1)$, $c = 31.555(3)$ Å, $\beta = 97.71(1)°$, $V = 4707.5$ Å^3; $Z = 4$. Data were collected on an automated CAD4 diffractometer ($Mo_{K\alpha}$), $2\theta \leq 47.0°$. 4976 absorption-corrected reflections ($I \geq 3\sigma(I)$). Atomic positions were obtained by Patterson and Fourier methods and refined using anisotropic temperature factors for Pt, Sn, Cl atoms and isotropic for the others. $R = 0.059$.

[6] a) J. H. Nelson, N. W. Alcock, *Inorg. Chem. 21* (1982) 1196; b) P. S. Pregosin, H. Rüegger, A. Albinati, R. Nägeli, *Angew. Chem. 94* (1982) 310; *Angew. Chem. Int. Ed. Engl. 21* (1982) 284; *Angew. Chem. Suppl. 1982*, 755–760; c) N. W. Alcock, J. H. Nelson, *J. Chem. Soc. Dalton Trans. 1982*, 2415.

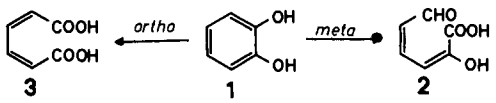
[7] General procedure: Solid $SnCl_2$ (9.5 mg, 0.050 mmol) was added to a solution of PPN$[PtCl_3(C_2H_4)]$ (43 mg, 0.050 mmol) in 1 mL CH_2Cl_2. The mixture was stirred for 0.5 h and then 5 mL petroleum ether (30–60°) added. The oily solid which precipitates was separated by decantation of the solvent, and then suspended in 10 mL petroleum ether (30–60°). After stirring for 15 h a yellow-brown suspension results which may be filtered to give the product. Yield 45 mg (85%). Anal. (calcd.): C, 43.04 (43.15); H, 3.18 (3.24); N, 1.37 (1.32); Cl, 16.85 (16.76).

Oxidative Cleavage of Pyrocatechol at the *meta*-Position; A Model Reaction for Cleavage by Pyrocatechol-2,3-dioxygenase?**

By *Rudolf Müller* and *Franz Lingens**

Dedicated to Professor Heinrich Hellmann on the occasion of his 70th birthday

Pyrocatechol **1** can be oxidatively cleaved in two different ways by enzymes: either between the hydroxy groups (*ortho*-cleavage) or adjacent to the hydroxy groups (*meta*-cleavage). The *ortho*-cleavage leads to *cis,cis*-muconic acid **3**, whereas *meta*-cleavage yields the relatively unstable 2-hydroxymuconic acid aldehyde **2**, which is easily recognized by its intense yellow color (λ_{max} (1 N NAOH) = 375 nm). Several model chemical systems have been



3 1 2

found for the *ortho*-cleavage, the majority of which involve the use of transition-metal complexes[1]. A non-enzymatic *meta*-cleavage, on the other hand, has so far never been reported in the literature. Herein, we wish to report how the *meta*-cleavage can be carried out in a purely chemical way, and how the structure of the unstable product thus formed has been established.

A solution of pyrocatechol in dimethyl sulfoxide (1 mg/mL) was added to a vigorously stirred solution of DMSO saturated with KO_2. The solution immediately turned blue, and after about 10 min at room temperature the color changed via green to yellow. At this point the reaction was terminated by a twofold addition of H_2O. After acidification with HCl the reaction mixture was extracted with CH_2Cl_2; the organic phase was then back-extracted with 0.2 N NaOH. For separation of residual DMSO and purification of the yellow compound, the alkaline solution was diluted tenfold with water and chromatographed on DEAE-cellulose with a NaCl-gradient (0–7.5%). The spectrum between 300 and 400 nm of the yellow fractions thus obtained corresponded to that of the product obtained on

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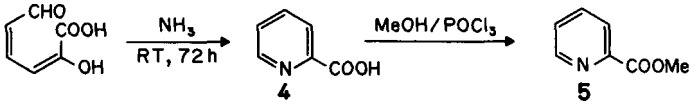
enzymatic *meta*-cleavage of pyrocatechol, both in alkaline solution ($\lambda_{max}=375$ nm) as well as in acid solution ($\lambda_{max}=316$ nm). Since **2** is relatively unstable it was treated with NH_3 for further characterization by the method of *Fujiwara* et al.[2]. After 3 days the yellow color



4 **5**

had disappeared and, as expected, the spectrum of picolinic acid **4** was obtained. The R_f value was identical with that of authentic picolinic acid, both in the thin-layer chromatography (toluene/dioxane/glacial acetic acid, 9:2:0.1) as well as in the HPLC (RP 8, 1% acetic acid). For final proof of the structure, the compound was esterified with methanol/$POCl_3$ according to the method described by *Klosa*[3]. GC-MS gave a peak whose retention time and mass spectrum (*m/z* 137, 4%, M^+; 107, 23%, $M-CH_2O$; 79, 100%, $M-COOCH_2$) were identical to those of methyl picolinate **5**.

The mechanism of the *meta*-cleavage with KO_2/DMSO is still unclear. Since the reaction does not take place under N_2 it can be concluded that not only hyperoxide and pyrocatechol but also molecular oxygen must participate, and that not just a simple reaction of hyperoxide and pyrocatechol is involved.

Several authors have discussed hyperoxide as a possible form of the reactive oxygen involved in dioxygenase reactions[4, 5]. This would infer that the above mentioned reaction could be a model for dioxygenase reactions.

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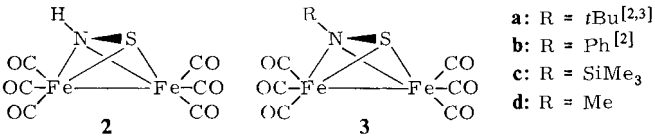
Sulfur Imide as *bisdihapto*-Bridging Ligand in the Complex $Fe_2(CO)_6(HNS)$**

By *Max Herberhold** and *Wolfgang Bühlmeyer*

The triatomic compound HNS is not known in the free state. According to ab initio calculations[1], of the two possible isomers, the sulfur imide **1a** is more stable than the thiazyl hydride **1b**.

1a **1b**

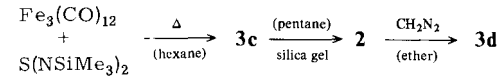
We report here on the binuclear iron complex $Fe_2(CO)_6(HNS)$ **2**, in which the sulfur imide **1a**, the parent of the (unstable) organic thionitroso compounds, is bound as a six-electron ligand.



2 **3**

a: R = *t*Bu[2,3]
b: R = Ph[2]
c: R = $SiMe_3$
d: R = Me

2 was synthesized by the stepwise degradation of bis(trimethylsilyl)sulfur diimide, $S(NSiMe_3)_2$, in the presence of carbonyliron complexes. Compounds of the type $Fe_2(CO)_6(RNS)$ **3** have previously been described[2,3]; the ligand is formed by fragmentation of sulfur diimides $S(NR)_2$ (R = *tert*-butyl[2,3], *p*-tolyl[3]) or sulfinylamines RNSO (R = phenyl[2]). In contrast to the known complexes **3a**, **b** the trimethylsilyl derivative **3c** is readily hydrolyzed; even chromatography on silica gel leads quantitatively to $Fe_2(CO)_6(HNS)$ **2**, which in turn can be methylated with diazomethane to **3d**[4].



Apart from the molecular ion at *m/z* 327 (rel. intensity 21%), the mass spectrum[5a] of **2** exhibits all the fragments $Fe_2(CO)_n(HNS)^+$ (n = 5–0) expected from stepwise cleavage of CO ligands; further fragments are $Fe_2(HNS)^+$ 159 (100%), Fe_2NS^+ 158 (23%), Fe_2S^+ 144 (16%), and Fe_2^+ 112 (10%). In addition to the CO bands, three absorptions at 3365 (s), 984 (m), and 760 (w) cm^{-1} occur in the IR solid-state spectrum (CsI), which are shifted to 2502, 806, and 729 cm^{-1}, respectively, upon deuteration (D_2O/pentane). The very sharp, intense band at 3365 cm^{-1} clearly corresponds to the NH stretching vibration, and we provisionally assign the band of medium intensity at 984 cm^{-1} to a deformation vibration involving displacement of the H-atom at the Fe_2NS tetrahedral skeleton upon variation of the HNS angle[5b]. The weak band at 760 cm^{-1} occurs in the region expected for NS single bond stretching vibrations (850–650 cm^{-1}); it is therefore ascribed to a skeletal vibration with considerable ν(NS) character. For **3a** and **3b** a ν(NS) absorption has been assigned (without supporting arguments) at 705 and 721 cm^{-1}, respectively[2]. Table 1 contains selected spectroscopic data for the new complexes **2** and **3c**, **d**.

Table 1. Spectroscopic data for the diiron complexes **2**, **3c**, and **3d**.

Complex	MS *m/z* (M_r)	IR [a] ν(CO) [cm^{-1}]	NMR [b] $\delta(^1H)$	$\delta(^{13}C)$
2	327	2080 s, 2040 vs, 2000 vs, 1995 s, 1985 m, 1978 w	[c]	—
3c	399	2072 s, 2032 vs, 1992 vs, 1986 s, 1976 sh, 1966 sh	0.25	1.03
3d	341	2074 s, 2034 vs, 1994 vs, 1988 s, 1980 sh, 1972 sh	3.40	52.5

[a] In pentane. [b] In $CDCl_3$, rel. TMS. [c] No ^{1}H-NMR signal in $CDCl_3$ (H/D exchange); in [D$_6$]benzene broad singlet at $\delta=2.15$.

The conspicuous similarity of the ν(CO) stretching frequencies and of the mass spectroscopic fragmentation behavior confirms the conclusion drawn from the reaction sequence **3c** → **2** → **3d** that the sulfur imide complex **2** is the parent compound of the thionitroso complexes **3**[6].

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CAS Registry numbers:
1a, 14501-19-0; **2**, 88253-20-7; **3c**, 88253-21-8; **3d**, 88253-22-9; $Fe_3(CO)_{12}$, 17685-52-8; $Fe_3(CO)_9S_2$, 22309-04-2; $S(NSiMe_3)_2$, 18156-25-7.

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[3] R. Meij, D. J. Stufkens, K. Vrieze, A. M. F. Brouwers, J. D. Schagen, J. J. Zwinselman, A. R. Overbeek, C. H. Stam, *J. Organomet. Chem. 170* (1979) 337.

[4] Preparation of **3c**: A solution of $Fe_3(CO)_{12}$ (200 mg, 0.4 mmol) and $S(NSiMe_3)_2$ (165 mg, 0.8 mmol) in 150 mL hexane is refluxed for 15 h. After removal of the solvent, **3c** can be isolated from the orange-brown residue by sublimation at 40°C/10^{-2} mbar: air-stable crystals, m.p. = 44—46°C; yield 80 mg (51%). The residue from the sublimation contains some $Fe_3(CO)_9S_2$[7].—Conversion **3c** → **2**: A solution of **3c** (80 mg, 0.2 mmol) in pentane was chromatographed under N_2 on a column (length 1.5 m, diameter 1 cm) packed with silica gel (Fluka, particle size 0.063—0.200 mm). Elution with pentane and crystallization yielded transiently air-stable crystals, m.p. = 46—49°C, which decompose slowly at room temperature. The reaction proceeds to completion.—Conversion **2** → **3d**: A *ca.* 3fold excess of diazomethane (Et_2O solution) is added to a solution of **2** (50 mg, 0.15 mmol) in 10 mL diethyl ether at 0°C and the solution stirred for 0.5 h. Air-stable crystals, m.p. = 30—32°C, can be obtained by sublimation. The reaction proceeds to completion. Yield 48 mg (92%).—The orange, diamagnetic complexes **2**, **3c**, and **3d** are readily soluble in polar and non-polar organic solvents and volatile *in vacuo* (10^{-2} mbar) even at room temperature.

[5] a) Varian CH7, direct inlet, 70 eV; temperature of the injector block 250°C, of the ion source 200°C. b) For comparison: For the molecules HNO and DNO stabilized in an argon matrix, the δ-vibrations have been assigned at 1110 and 882 cm^{-1}, respectively: D. E. Milligan, M. E. Jacox, S. W. Charles, G. C. Pimentel, *J. Chem. Phys. 37* (1962) 2302, and references cited therein.

[6] Apart from the dinuclear complexes $Fe_2(CO)_6(RNS)$ (**3**) containing derivatives of sulfur imide described here, some mononuclear complexes $Cr(CO)_5(RNS)$ are known in which the substituent R is also bonded to the nitrogen atom ($R = NMe_2$, NPh_2): cf. H. W. Roesky, R. Emmert, W. Clegg, W. Isenberg, G. M. Sheldrick, *Angew. Chem. 93* (1981) 623; *Angew. Chem. Int. Ed. Engl. 20* (1981) 591; H. W. Roesky, R. Emmert, W. Isenberg, M. Schmidt, G. M. Sheldrick, *J. Chem. Soc. Dalton Trans. 1983*, 183.

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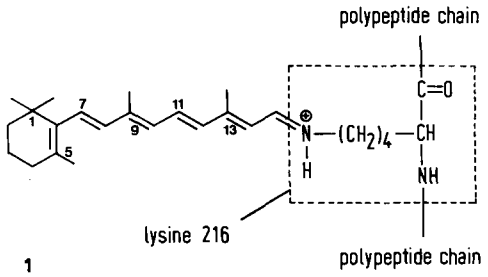
Sterically Fixed Retinal-Analogue Prevents Proton-Pumping Activity in Bacteriorhodopsin

By *Elisabeth Kölling**, *Wolfgang Gärtner*, *Dieter Oesterhelt*, and *Ludger Ernst*

Bacteriorhodopsin (BR), the dominating membrane protein of *Halobacterium halobium*, contains 13-*cis*- and all-*trans*-retinal as prosthetic groups. The retinal molecule forms a protonated Schiff's base (SBH^+) **1**[1] with the ε-amino group of the lysine residue 216 of the apoprotein.



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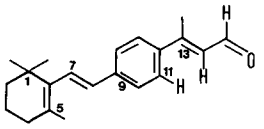
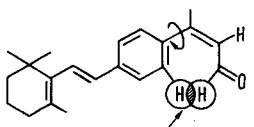
Irradiation of BR ($\lambda_{max} = 568$ nm) induces a photochemical cycle during which numerous intermediates could be detected spectroscopically (BR_{trans}-568 → K-610 → L_{cis}-550 → M_{cis}-412 → O-660 → BR_{trans}-568; absorption maxima in nm)[2]. These species are formed inter alia by deprotonation/reprotonation of the SBH^+ and by all-*trans*-/13-*cis*-isomerization of the retinal molecule[3]. Steric and electronic constraints in the protein permit the thermal back reaction from the 13-*cis*-(M_{cis}-412) to the all-*trans* form (BR_{trans}-568) in the cycle to which a directed proton transport is coupled, i.e. bacteriorhodopsin functions as a "light-driven proton pump".

Modified retinals can be incorporated into the apoprotein isolated from retinal-negative cell mutants and can be tested for their functional activity. As a result, a strong influence specifically associated with substitution at C-13 of the retinal with both chromophore and function of the protein was found. In particular, in analogues carrying no 13-methyl group the reisomerization 13-*cis*- → all-*trans* is so disturbed that the proton transport is drastically retarded[4].

We prepared the retinal analogue **2** (3-[4-[2-(2,6,6-trimethylcyclohexenyl)vinyl]phenyl]-2-butenal) from the acid by reduction ($LiAlH_4$)/oxidation (MnO_2) and characterized it spectroscopically (^{1}H-NMR, IR, MS, UV). **2** can be considered as a 10,11-s-*cis*-fixed retinal bridged between C-9 and C-12, which contains an aromatic ring as novel structural element (atoms numbered as in retinal). Whereas the all-*trans*-isomer **2a** is predominantly planar in solution, the 13-*cis*-isomer **2c** can only be formed because of steric hindrance if simultaneous rotation of the 12,13-single bond occurs, as shown in the formula.



all-*trans*-isomer **2a**



13-*cis*-isomer **2c**

Irradiation of **2a** in isopropyl alcohol affords 7-*cis*-**2b** and the 13-*cis* compound **2c**, which occur in photostationary equilibrium (10 min irradiation) in the ratio 20 : 13 : 67. The assignment followed by 400 MHz ^{1}H-NMR spectroscopy after HPLC separation (Table 1). The 7-*cis*-13-*cis*-isomer could not be detected.

Table 1. ^{1}H-NMR data of compounds **2a** (all-*trans*), **2b** (7-*cis*), **2c** (13-*cis*), and all-*trans*-retinal (in $CDCl_3$). δ-values, J in Hz.

	13-Me	H-7	H-8	Aryl	H-14	H-15
	^4J(13-Me,14)		^3J(7,8)			^3J(14,15)
2a	2.57	6.81	6.35	7.49	6.43	10.10
	1.2		16.4		7.9	
2b	2.55	6.18	6.42	7.47	6.43	10.18
	1.3		12.5		7.9	
2c	2.32	6.77	6.37	7.27/7.44	6.13	9.54
	1.4		16.3		8.1	
Retinal	2.32	6.33	6.15	—	5.96	10.09
	1.2		16.0		8.1	

The *trans*-configuration of the 13,14-double bond of the 7-*cis*-isomer **2b** was determined by a nuclear Overhauser effect (NOE) experiment (irradiation of the 13-methyl re-

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sonance effects an increase in intensity of the aldehyde signal). The low-field shift (ring current effect) of the 13-methyl protons in 7-*cis*-**2b** and in the all-*trans*-isomer **2a** relative to the chemical shift of these protons in the 13-*cis*-form and in retinal itself indicates that the aromatic ring and the 13,14-double bond vinyl group are coplanar. Due to the diamagnetic anisotropy of the carbonyl function, the aryl protons in the 13-*cis*-compound **2c** give rise to an AA'BB' spectrum; in addition, the signal of the aldehyde proton appears at a higher field than that of the all-*trans*-isomer **2a**, in accord with literature data for *cis*- and *trans*-β-methylcinnamaldehyde[6]. The NMR data in Table 1 indicate a conformation for the 13-*cis*-isomer **2c** in which rotation about the 12,13-single bond causes the chain end to protrude out of the plane of the aromatic ring.

Only the all-*trans*-compound **2a** reconstitutes with isolated apoprotein a protonated Schiff's base within a few minutes, which results in a bathochromic shift of the absorption maximum to 490 nm (Table 2). The preparation containing the 13-*cis*-sample **2c** was left at room temperature for several hours and showed only a slow isomerization to the all-*trans*-form, accompanied by the formation of a chromophore with absorption maximum at 490 nm. This could be detected by extraction of the retinal analogues from the protein and subsequent determination of the isomer distribution. Compound **2** is the first retinal analogue which in its 13-*cis*-configuration does not fit into the binding site of bacteriorhodopsin. This can only be explained by the non-planar arrangement of C-11 to C-14. A corresponding thermal isomerization of the 7-*cis*-compound **2b** was not observed; the reconstitution occurred only after irradiation ($\lambda_{max} = 490$ nm). From all of these reconstituted samples, also after irradiation experiments (up to 30 min), exclusively the all-*trans*-isomer **2a** was isolated.

Table 2. Absorption maxima of compounds **2a**, **2b**, **2c**, all-*trans*-retinal, and the associated protonated Schiff's bases *n*-Bu−$\overset{\oplus}{N}$H=CHR with *n*-butylamine and the bacteriorhodopsins.

	Retinal or analogues λ_{max} [nm] (ε) [a]	Prot. Schiff's base λ_{max} [nm] ($\tilde{\nu}_1$ [cm^{-1}]) [a]	Bacteriorhodopsin λ_{max} [nm] ($\tilde{\nu}_2$ [cm^{-1}]) [b]	$\tilde{\nu}_1 - \tilde{\nu}_2$ [cm^{-1}] ([kJ mol^{-1}])
2a	330 (20000)	380 (26320)	490 (20410)	5910 (70.7)
2b	323 (10000)	372	—	—
2c	305 (11000)	365	—	—
Retinal	380 (40000)	440 (22730)	568 (17610)	5120 (61.3)

[a] In isopropyl alcohol. [b] In water.

The absorption of the protonated Schiff's base in the protein is bathochromically shifted relative to the protonated Schiff's base with *n*-butylamine. This decreased energy difference between the ground and the excited state, when estimated by the difference of the according wave numbers—see Table 2—is found to be 5180 cm^{-1} (61.3 kJ·mol^{-1}) for retinal, and 5910 cm^{-1} (70.7 kJ·mol^{-1}) for analogue **2**. From the similar difference in wavenumbers ($\tilde{\nu}_1 - \tilde{\nu}_2$) (cf. Table 2) for retinal and the analogue **2** it can be concluded that similar interactions with the binding site of the protein take place.

As indicated by functional investigations with cell vesicles, the chromophore formed from compound **2** and bacterioopsin does not facilitate proton pumping activity. In addition, no bleaching at 490 nm could be observed in studies of the photocycle with ns laser pulses in the isolated, reconstituted protein. Both those results illustrate the necessity of an all-*trans*-/13-*cis*-isomerization for the function of bacteriorhodopsin. This conclusion is corroborated with retinal analogues whose configuration was fixed at the 13,14-double bond by bridging[7].

Analogue **2a** requires room for the 13-methyl group either above or below the polyene chain in order to isomerize into the 13-*cis* form (**2c**), due to the fixed 10,11-s-*cis* bond and the associated rotation of the 12,13-single bond. This space, however, is apparently not available in the protein (no 13-*cis*-isomer in the protein). Thereby, it can be deduced that—as a prerequisite for proton translocation in bacteriorhodopsin—steric hindrance of the protein permits an all-*trans*/13-*cis*-isomerization upon irradiation and, at the same time, reinforces the thermal reisomerization.

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CAS Registry numbers:
2a, 88296-58-6; **2b**, 88296-59-7; **2c**, 88296-60-0; retinal, 116-31-4; H^+, 12408-02-5.

[1] D. Oesterhelt, W. Stoeckenius, *Nature New Biol. 233* (1971) 149.
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Hexa-*O*-alkanoyl-*scyllo*-inositols, the First Alicyclic, Saturated, Discotic Liquid Crystals**

By *Bernd Kohne* and *Klaus Praefcke**

Dedicated to Professor Alexander Schönberg on the occasion of his 91th birthday

In 1977 the occurrence of a thermotropic mesophase was reported for certain hexaalkanoyloxy derivatives of benzene[1], and hence the possibility of forming mesophases of pure compounds having disc-like molecular structures ("disk-like mesogens") was demonstrated for the first time. Since then, further liquid crystals of compounds with related structures have been prepared[2]; their rigid, planar molecule centers are π-systems of various structures, mainly arenes substituted with flexible side chains. A notable exception is diisobutylsilanediol dimer, whose core consists of a *saturated* but thermolabile hetero-

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cycle formed by conventional hydrogen bonding, which as early as 1955 was described as a liquid crystal[3a], but whose mesophase was first recognized in 1981 as thermotropic discotic[3b].

Substitution of the 1,4-disubstituted phenyl moieties in numerous calamitic liquid crystals ("rod-like" mesogens) by cyclohexyl groups[4], frequently leads to compounds which exhibit improved physical properties for electrooptical applications. This induced us for the first time to study the influence of analogous constitutional changes on the liquid-crystalline properties of *discotic* systems.

We therefore synthesized[5] the first alicyclic, saturated, discotic liquid crystals, the three hexa-*O*-alkanoyl-*scyllo*-inositols **1a–c** — perhydrogenated analogues of known benzene derivatives[1]. Their phase transition data are summarized in Table 1, and their phase transition temperatures are shown in Figure 1 to illustrate the extent of their mesophase regions as a function of chain length.

1a, R = n-$C_5H_{11}CO$
1b, R = n-$C_7H_{15}CO$
1c, R = n-$C_9H_{19}CO$

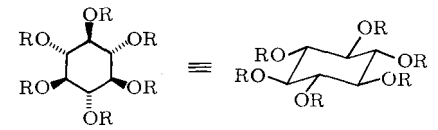

Table 1. Phase transition temperatures [a] and phase transition enthalpies [b] (ΔH) of the cyclohexane derivatives **1a–c**.

	M.p. [°C] (C→D)	Clar. pt. [°C] (D→I)	Stabile mesophase region ΔT [°C]	ΔH [kJ/mol]p C→D	D→I
1a	68.5	199.5	131.0	21.15	8.84
1b	75.5	198.5	123.0	43.30	9.47
1c	84.0	188.7	104.7	53.07	10.28

[a] Polarizing microscope with Mettler hot stage FP2. [b] DSC Du Pont 1090; phase transitions, crystalline→discotic (C→D) or discotic→isotropic (D→1).

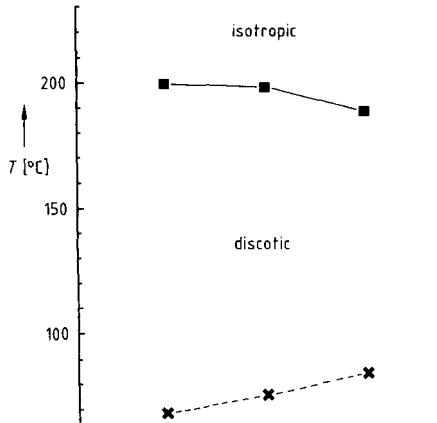

Fig. 1. Phase transition temperatures of the hexa-*O*-alkanoyl-*scyllo*-inositols **1a–c** (× crystalline→discotic; ■ discotic→isotropic; n = number of alkyl carbon atoms of the groups R in **1**).

In contrast to **1a** and **1c**, their benzene analogues are not liquid crystalline; only the benzene analogue of **1b** exhibits a narrow mesophase region ($\Delta T \approx 6$ °C)[1]. The hexasubstituted triphenylene corresponding to **1a** also is not a liquid crystal[6]; whereas the triphenylene derivatives with similar side-chains to **1b** and **1c** exhibit mesophase regions which are only *ca.* half as wide ($\Delta T \approx 60$ and ≈ 50 °C, resp.)[6]. These comparisons demonstrate that the hexasubstituted cyclohexanes with the stereochemistry given in **1** are considerably superior to analogous benzene or triphenylene derivatives in terms of both formation and width (ΔT) of thermodynamically stable mesophases.

Inspection of space filling models indicates that benzene derivatives are considerably less spatially demanding in the middle section than the corresponding cyclohexane compounds **1a–c**, which have an ideal disk shape. According to our findings, the core of a discotic liquid crystalline compound can either be saturated or unsaturated; of greater importance for the formation of discotic mesophases are space filling (minimum dead space), planarity, and rigidity of a molecule.

Hitherto, the type of mesophase formed from **1** has not yet been classified. Preliminary microscopic observations of **1** between crossed polars, however, indicate hexagonal, columnar phases. Heating compounds **1** above their melting points affords viscous highly birefringent phases whose textures are smectic-like phases. Upon cooling the isotropic liquids below the phase transition temperatures (I→D) less birefringent finger- or fan-shaped regions appear in a predominantly black surrounding field in which the molecules are apparently orientated plano-parallel to the surface of the cover slip.

Because of their weak UV absorption (e.g., **1b**: $\lambda_{max} = 211$ nm ($\varepsilon = 357$ L·mol^{-1}·cm^{-1})), these *scyllo*-inositol derivatives **1** may be suitable anisotropic, discotic matrices for the spectroscopic study of aromatic molecules.

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CAS Registry numbers:
1a, 88269-10-7; **1b**, 88211-15-8; **1c**, 88211-14-7; *scyllo*-inositol, 488-59-5; octanoyl chloride, 111-64-8.

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[5] Procedure using the example of the synthesis of **1b**: *scyllo*-inositol (180 mg, 1 mmol) is stirred with a slight excess of a solution of octanoyl chloride in trifluoroacetic acid for 2 h at room temperature; after flash chromatography (twice) of the crude product on 30 g silica gel 60 (230–400 mesh, Merck) with hexane/ethyl acetate (20+1) and two recrystallizations from ethanol/acetone (*ca.* 5+1), 690 mg (74%) pure **1b** was obtained as colorless, fine needles (for phase transition data see Table 1 and Figure 1). Further data for **1b**: IR ($CHCl_3$): $\nu = 1762$ cm^{-1} (CO); ^{1}H-NMR ($CDCl_3$, Bruker WM 400): $\delta = 0.87$ (t, $J \approx 7$ Hz, 18H, CH_3), 1.19–1.31 (m, 48H, CH_2), 1.45–1.55 (m, 12H, β-CH_2), 2.19 (t, $J \approx 7.5$ Hz, 12H, α-CH_2), 5.25 (s, 6H, *tert*-H); ^{13}C-NMR ($CDCl_3$, Varian CFT 20): $\delta = 14.0$ (q, CH_3), 22.6, 24.9, 29.0, 29.2, 31.7, 34.0 (t, 6CH_2), 70.0 (d, ring-C), 172.2 (s, CO); $C_{54}H_{96}O_{12}$ (937.3), calc. C 69.19, H 10.32%, found C 69.55, H 10.02%. **1a** and **1c** are obtained analogously; their structures are confirmed as **1b** from spectroscopy and elemental analysis.

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The Electrochemical Reduction of Benzene—First Direct Determination of the Reduction Potential**

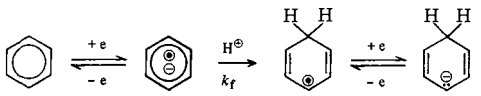
By *John Mortensen* and *Jürgen Heinze**

The physical and chemical properties of benzene have been studied in more detail than those of any other organic compound. It is therefore all the more surprising that its electrochemical reduction potential in solution could not previously be measured directly. This is mainly because of the extremely low electron affinity of benzene[1], which to a great extent precludes reduction in the stability range of the commonly used supporting electrolytes and solvents.

Gerson et al.[2] determined the reduction potential of benzene by extrapolating the electrolytically determined appearance potentials of the radical anions of twenty hydrocarbons. They obtained a value of -3.31 ± 0.12 V vs. SCE. More recently, *Jund, Lemoine,* and *Gross*[3] corroborated the assumption that the reduction potential of benzene lies below -3.3 V.

We have now been able to directly determine the reduction potential of benzene via voltammetric measurements (-60 °C) at a Pt working electrode under "super-dry" conditions in dimethoxyethane (DME) in the presence of tetrabutylammonium hexafluorophosphate ($TBAPF_6$) as supporting electrolyte. Evaluation of the cyclic voltammogram (CV) affords a value of -3.42 ± 0.05 V vs. SCE.

As indicated by the blank voltammogram of the system DME/$TBAPF_6$ at -60 °C, decomposition of the conducting electrolyte commences at -3.46 V, and hence the reduction wave of benzene lies partly in the increasing current range of the conducting electrolyte. This explains why attempts failed to measure the reduction potential directly. At slow scan rates (*ca.* 100 mV/s), the voltammogram indicates a homogeneous chemical follow-up reaction of the initial radical anion **1b**. Presumably, by analogy to other highly charged arene anions[4], the strongly basic anion **1b** attacks the tetrabutylammonium ion and is protonated via Hofmann elimination. The cyclohexadienide **1d**, whose reoxidation can be detected by CV at -0.5 V, is formed from the neutral radical **1c** by further electron transfer.



1a **1b** **1c** **1d**

The observed reduction wave therefore corresponds to a two-electron transfer with a coupled chemical reaction (ECE mechanism); a similar reaction pathway has been observed with [2.2]paracyclophane. Evidence for the ECE mechanism postulated is provided by the fact that the current-function $i/\sqrt{v}$ decreases with increasing scan rate.

Because of the extreme value of the potential for the reduction of **1a** to **1b**, reaction of **1b** with the products arising from the electrochemical decomposition of the tetrabutylammonium ion is, in principle, conceivable. However, in this case the neutral radicals formed from the cation of the conducting salt should decay considerably faster than is observed experimentally. If the scan rate is increased, then at 20 V/s a flat wave appears in the reverse scan of the voltammogram which establishes the increasing stability of the benzene radical anion on the time-scale of the experiment (Fig. 1a). However, because of the low conductivity of the electrolyte system the resulting non-compensated IR-drop strongly distorts the current-potential curves. For this reason, we simulated the cyclic voltammogram assuming a non-compensated resistance of 0.8 kΩ using a newly developed algorithm[5]. Under the given conditions—decomposition of the conducting salt above -3.46 V—there is very good agreement with the experimental results (Fig. 1b). With the aid of the simulation, the rate constant of the follow-up reaction at -60 °C in DME was determined as $k_f = 19 \pm 5\ s^{-1}$.

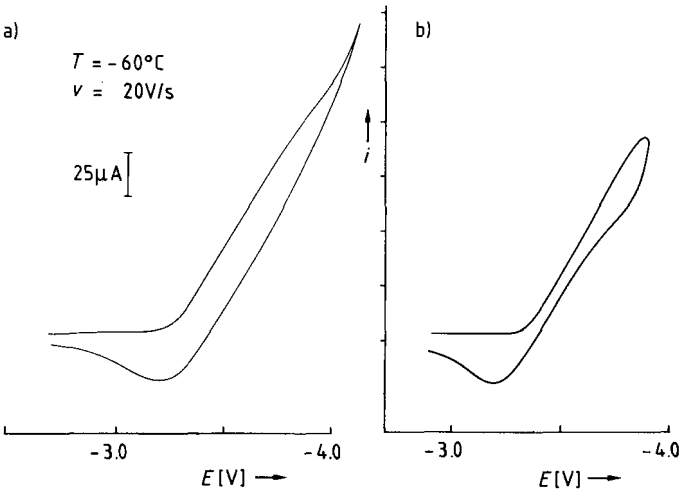


Fig. 1. a) Experimental CV diagram for the reduction of **1a** in DME; b) simulated CV diagram ($v = 20$ V/s, $k_f = 19\ s^{-1}$, $T = -60$ °C) without potential correction, current axis in arbitrary units.

Because of the *iR*-drop, the experimental and simulated values of the potential cannot be directly correlated with the reference electrode (SCE). However, the actual potentials can be deduced from the simulation.

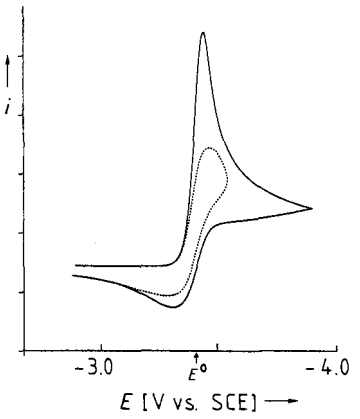


Fig. 2. Potential-corrected, simulated CV diagram ($v = 20$ V/s); -----: without *iR* compensation, ———: with *iR* compensation, current axis in arbitrary units.

Figure 2 shows the simulated CV diagram for the reduction of benzene at 20 V/s, calculated with and without *i*R compensation by "correct" representation of the potential axis. The value of the redox potential can be read directly

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from the voltammogram using known criteria. The maximum current ratio i_{ap}/i_{cp} deviates from unity and indicates the subsequent reaction on the time-scale of the measurements.

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BOOK REVIEWS

Atomic Spectrometric Trace Analysis. Edited by *B. Welz*. Verlag Chemie, Weinheim 1982, xvi, 564 pp., bound, DM 148.00

This conference report deals with 55 contributions which were presented at the 1st Colloquium on "Trace Analysis by Atomic Spectrometry" (Konstanz, April 7 to 9, 1981).

The increasing importance of reliable techniques for the determination of low and lowest element concentrations (ng/g to pg/g range) in many areas of the geological, biological, materials sciences and in medicine, as well as environmental control, has made large, close, interdisciplinary exchange of views concerning the currently available methods, their capabilities and their limitations desirable. The conference and the book resulting from it admirably meet these requirements. The conference was organized by an instrument manufacturing company (Bodenseewerk Perkin-Elmer GmbH, Überlingen) rather than by a scientific institute, as is more usually the case. Perhaps, this unusual circumstance is the reason why a valuable evaluation of the actual problems of trace analysis came about. Some important techniques in atomic spectroscopy used today, such as atomic absorption spectroscopy, enabling single element determinations, and optical emission spectrometry with high frequency plasma excitation (ICP-AES) for multielement determinations are considered. Their performance as well as their limitations are discussed, mainly from the point of view of the user. Most of the contributions are devoted to the solution of practical problems. With regard to the type of samples, biological materials and water samples take pride of place. The trace elements concerned tend to be the "old friends", namely Hg, Cd, Pb, Tl, Se and As and the motivation for their determination and analytical strategies to be applied are relatively uniform. Specialized topics concerning trace analysis of Si, As, Sn and organotin compounds, alkyl lead compounds as well as vapor phase lanthanoids and actinoids introdue some variety.

However, there is still a long way to go before universal and, at the same time, reliable and highly characteristic instrumental methods are available which make the direct analysis of solid samples possible. Therefore, decomposition and separation techniques which are employed prior to the actual determination are of great importance. In this connection, the reader will find very informative review articles on the decomposition of organic matrices by *G. Knapp* and on removal of the matrix by *E. Jackwerth*.

From the point of view of the development of instrumental methods of determination, the following contributions are particularly valuable: "A comparison of the various Zeeman systems in AAS" by *L. de Galan* and *M. T. C. de Loos-Vellebregt*, "Forward scattering—a method for multielement determination" by *P. Wirz* and *A. Scharman*, "Loop AAS and AES": a new, highly sensitive micromethod for flame AAS and AES" by *H. Berndt* and *J. Messerschmidt*. A further paper submitted by the editor and his co-workers and relates to improvements in standardization of graphite tube AAS by a better separation of peaks and to the hydride AAS technique.

This conference report is first of all a collection of experiences which can be thoroughly recommended for analysts involved in trace element analysis with the aid of spectroscopy. It further displays inadequacies to be overcome by scientists involved in the development of methods. Finally, it gives a good insight into the multiplicity of current problems in this field; this is useful to those who are less initiated—amongst whom I include the coming generation of analysts. However, the disproportionally high price of the well-edited, photo-reproduced volume will oppose my positive recommendation to acquire it.

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The Pyridine Nucleotide Coenzymes. Edited by *J. Everse, N. Anderson,* and *K.-S. You*. Academic Press, New York 1982, xxxv, 389 pp., bound, $ 46.00

Commemorative works are often primarily concerned with the reputation of the commemoratee (and often of the author) and seldom apply themselves to the information requirement of the reader. This book on pyridine nucleotides, published to commemorate the 75th birthday of *Nathan O. Kaplan*, demonstrates that this need not necessarily be the case. *Kaplan* was one of the pioneers of enzymology and, above all, of the synthetic chemical treatment of this class of coenzymes, which *Otto Warburg* discovered in the nineteen thirties. *Kaplan*'s merits in this research area and his efforts as teacher and scientific organizer are introduced by experienced and famous pens. *M. D. Kamen, F.*

Lipmann, W. D. McElroy, and *S. P. Colowick* acquaint us not only with the personality of the scientist, *Kaplan,* but also with the stages of his development and the background against which his remarkable achievements unfolded.

Colowick's remarks introduce the reader in a subtle way to the theme of the book, which, in ten chapters, treats evolutionary aspects of pyridine nucleotides as well as the physico-chemical, synthetic chemical and cell-biological aspects of NAD and NADP. The classical enzymology of the dehydrogenases developed by *Warburg* and his school is scarcely mentioned. This approach is only applied in the case of membrane-bound catalysts and non-redox processes with NAD. The functional aspects are dealt with in terms of X-ray structural analysis together with the application of pyridine nucleotide analogues and of immobilized coenzymes. None of the chapters seeks to be encyclopedic in its completeness, the most important problems are, nevertheless, discussed and enriched with a literature selection that is usually representative.

In the first chapter, *H. B. White III* develops ideas concerning prebiotic origins and the mode of action of pyridine nucleotides in the early stages of evolution. Structural features of dehydrogenases, such as the similarity of their domain structures, are discussed in support of the hypothesis that it was the polypeptide structures that adapted to the primitive pyridine nucleotide "dehydrogenases" (a very plausible but not generally accepted assumption).

The second chapter *(J. B. A. Ross, S. Subramanian, L. Brand)* describes the present state of knowledge concerning the electronic structure of pyridine nucleotides and their analysis by absorption, CD, fluorescence and phosphorescence spectroscopy. The chemistry of NAD and NADH, together with various homologues and analogues as well as their conformations in solution, are dealt with by *N. J. Oppenheimer* in the third, and the synthesis, properties and applications of a large number of synthetic coenzyme analogues by *B. M. Anderson* in the fourth chapter. Since this was *Kaplan*'s field of research for almost 30 years it is not surprising that these topics are given, with more than 80 pages, an importance that seems a little disproportionate.

In the fifth chapter *U. M. Grau* presents, with many clear schemes, a very good description of the interactions of the pyridine nucleotide coenzymes with the apodehydrogenases, insofar as they can be deduced from X-ray structural analysis data. The most important aspects of a fascinating chapter of structural research on enzymes is given in a condensed but up-to-date form.

The sixth chapter *(C.-Y. Lee, A. F. Chen)* offers a valuable review to those who are concerned with the problems of the immobilization of dissociable coenzymes, naturally with special emphasis on NAD and NADP. Synthetic coupling techniques, general aspects of ligand affinity chromatography and numerous examples of application are presented.

The seventh chapter by *H. B. White III* summarizes the present state of knowledge concerning biosynthesis, interconversion, degradation and excretion of pyridine nucleotides and their secondary metabolites. In the eighth chapter *M. B. Grisham* and *J. Everse* deal with the role of pyridine nucleotide oxidases in the formation of activated oxygen species during phagocytosis.

Chapter 9 from the pens of *R. R. Fisher* and *S. R. Earle,* summarizes the available information on membrane-bound transhydrogenases concerned with electron transport in microorganisms and mitochondria, including the problem of energy coupling. In the last chapter *P. H. Pekala* and *B. M. Anderson* discuss those reactions where NAD is not a redox partner but a substrate: the mono- and poly-ADP-ribosyl transfer to proteins. The former concerns, besides the NAD-glycohydrolases, above all the chemical modification of regulatory proteins triggered off by toxins (cholera, diphtheria, *etc.*); the latter processes occurs in the cell nucleus and seems to influence DNA repair and DNA synthesis during differentiation and during the cell cycle.

This well-produced book, which is provided with an index, can offer biochemists, biophysicists and cell biologists new as well as established material in a clear and competently discussed form. Its up-to-date character recommends it to the teacher as well as to the advanced student and the active research worker. The price may be high but not inappropriate for what is offered.

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Electron Distributions and the Chemical Bond. Edited by *P. Coppens* and *M. B. Hall.* Plenum Press, New York 1982. ix, 479 pp., bound, $ 55.00

The Spring 1981 Meeting of the American Chemical Society held at Atlanta, GA, included a Symposium dealing with Electron Distributions and the Chemical Bond. This book is the written account of the lectures presented at the Symposium. Its 21 chapters cover a wide range of topics all concerned in one way or another with charge densities in molecules or in extended solids as obtained either experimentally from X-ray diffraction measurements or theoretically from quantum-mechanical calculations. Both of these approaches have made enormous advances over the last decade or so, but each of them also has its own built-in deficiencies. Fortunately, the errors and approximations inherent in the one approach are virtually independent of those in the other, and it is clearly in the confrontation between theory and experiment that the Editors of this book expect its main interest to lie. As far as one can judge, where high-quality comparisons are available for molecular systems containing only light atoms (say, up to F) the results agree rather well. However, the confidence that might be generated by such comparisons does not necessarily extend to studies of systems containing heavier atoms which are much more difficult either to measure or to compute reliably.

As with most books based on Conference proceedings, the quality of the individual chapters is very uneven. Among the more valuable contributions should be mentioned those of *Smith* (on theory), of *Coppens* (on the experimental approach, and including a useful glossary of terms that should help newcomers to follow the jargon), and of *Breitenstein et al.* (on comparison of experiment and theory). The article by *Irngartinger* gives a good idea of what can be learned from careful experimental electron-density studies of organic molecules. At the other end of the scale, some of the contributions appear to be at best of merely anecdotal interest. One article that can hardly fail to raise a few eyebrows is that by *Troup, Extine* and *Ziolo* on electron-density studies on tellurium compounds. Doubtless some people will be impressed by their claim to have obtained experimental evidence for bonding density features such as lone pairs in heavy-atom systems, but many others will find it difficult to see how the conclu-

sions presented by these authors can possibly stand up to critical scrutiny of the evidence. Presumably, the lecture itself provoked some lively discussion, and it seems perhaps a pity that only one side of the story is presented in the printed proceedings.

Several chapters mention the theorem due to *Hohenberg* and *Kohn*, according to which all ground-state properties of any system, including the wave function, are functionals of the charge density distribution, *i.e.* they can be calculated in principle from a knowledge of the charge density. The "in principle" is important, because nobody so far seems to actually know how to calculate these functionals. However, since the charge density is an observable while the wave function is not, the Hohenberg-Kohn theorem and its repercussions (discussed in the chapter by *Parr*) may help to explain why interest among experimentalists and theoreticians in charge-density studies of molecules and extended systems is so lively. The publication of this book is an expression of this interest. From it, the reader can hope to find some of the questions that are being asked in the area as well as some of the answers that are being given.

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Covalent Catalysis by Enzymes. By *L. B. Spector*. Springer-Verlag, Berlin 1982, xii, 276 pp., bound, DM 78.00

Covalent enzymic catalysis (double displacement) has been known for a long time. It is accepted as a guiding principle, almost without exception, in the mode of action of vitamins as enzyme cofactors, that the chemical process of substrate reaction takes place on the vitamin unit. Some of these cofactors are covalently bound to their apoenzyme; knowledge of covalent enzymic catalysis stretches back more than half a century.

In 1971 *R. M. Bell* and *D. E. Koshland* compiled a list of 60 enzymes where the application of critical criteria revealed a high likelihood of covalent catalysis. A little later this figure was raised to 140 by *L. B. Spector*, and the much more thorough-going claim was made that all enzyme catalysis proceeds *via* covalent enzyme-substrate intermediates. The present monograph is an attempt to strengthen this concept.

It would have been a good idea to acquaint the reader with the criteria for direct reaction between substrates (single displacement; kinetic sequential; stereochemical inversion of configuration) together with their alternatives (double displacement; kinetic ping-pong; stereochemical retention of configuration; exchange reactions in the absence of the second substrate; isolation of an enzyme substrate complex and demonstration of its kinetic competence). There is only inconclusive kinetic evidence for single displacement without discernible stereochemical consequence. The author founds his assertion that all catalysis is covalent thus: "Single displacement is purely speculative, because no positive evidence in support of it exists. For the documentation of this statement I can do no more than refer the reader to the whole corpus of chemical literature on the chemical mechanism of enzyme action."

The experimenter is faced with a difficult problem in demonstrating direct interaction between the substrates; he must exclude covalent catalysis by every possible test, of necessity this means negative results, thus completing a vicious circle. This, however, does not mean that single displacement reactions do not exist as this author so vehemently insists. Inversions of configuration which indicate direct reaction of the substrates are craftily interpreted by the author as triple displacements. This may be the case but it has not been demonstrated. What is certain is that the examples cited (acetate kinase, adenosine-phosphoribosyl transferase) are insufficient to lead to a conclusion.

It would have been a good idea to acquaint the reader with examples that mimic covalent catalysis: exchange reactions with a substrate may result from a second substrate being firmly attached to the enzyme; a substrate alone may become covalently attached to the enzyme in a side reaction; unphysiological substrate analogues (e.g. suicide inhibitors) may form covalent enzyme substrate bonds when the physiological substrate does not. Finally, some isotope labeling experiments that purport to demonstrate covalent attachment can be attributed to faulty control experiments.

Conclusions that catalysis is covalent are only convincing when all the criteria are fulfilled or when a deviation can be explained. It lies in the nature of a claim that all catalysis is covalent, that the author ignores this critical illumination and does not adequately distinguish experimental demonstration from experimental indications. It can be left to the reader to check the significance of the results described and to decide whether he is reading "covalent catalysis above all" or "above all covalent catalysis".

In this spirit it is possible to recommend this book, which is deliberately provocative, lively and, on occasions, informative, to everyone with an interest in the mechanism of enzymic reactions.

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Methods in Stereochemical Analysis I. Stereochemical Applications of NMR Studies in Rigid Bicyclic Systems. By *A. P. Marchand*, Verlag Chemie International, Deerfield Beach 1982, 231 pp., bound, DM 280.00

This book is the first of a new series of monographs to be edited by the author, which is to cover the application of NMR, together with other spectroscopic and physical methods, to stereochemical problems.

This first volume is devoted to the NMR spectroscopy of the bicyclo[2.2.1]heptanes and the [2.2.2]octanes, which have achieved great importance, not only as models for spectroscopic investigation but also for preparative and mechanistic studies, since these rigid molecules are particularly suitable for stereochemical studies.

The book is divided into three chapters. The first chapter presents methods of signal assignment and discusses them in detail using examples. The chapter begins with a study of the application of lanthanoid shift reagents in the evaluation of ^{1}H-NMR spectra, where the theoretical background is largely ignored; then the homo- and heteronuclear nuclear Overhauser effect (NOE) is introduced. A word of criticism is pertinent at this point. Even though this monograph does not aim to discuss measuring techniques, the enormous refinement of NMR techniques in recent years makes it desirable to discuss assignment aids somewhat more fully. This is particularly the case since it

cannot be the aim of this book only to review the methods that have been described for bicyclic systems, but should also stimulate further investigations applying the most modern of possibilities.

The second chapter covers stereochemical applications of chemical shifts in several nuclei (^{1}H, ^{13}C, ^{19}F and ^{31}P); first steric effects then electronic substitution effects are discussed in terms of their dependence on the stereochemistry of the molecule. The tabular presentation of some of the conclusions from investigations on various types of compounds is particularly clear. The correlation of chemical shifts with charge density for a large number of bicyclic carbonium ions is discussed at the end of this chapter; the results are again collected in tabular form.

The third chapter, which makes up by far the largest portion of the book, deals with the measurement and interpretation of spin-spin couplings. A short, general introduction is followed successively by discussions of homo- and heteronuclear coupling over, one, two, three, four and more bonds, with a plentiful supply of data listed to illustrate each case.

There is no doubt that this book fills a vacant niche in the review literature and will provide any chemist who is in some way concerned with compounds of this class with a wealth of valuable information. It should be included in any balanced NMR library. However, it is to be feared that, in the present financial climate, the unusually high price will prevent the wide dissemination that the book deserves.

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Metal-Carbon and Metal-Metal Multiple Bonds as Ligands in Transition-Metal Chemistry: The Isolobal Connection

By F. Gordon A. Stone*

A new domain for synthesis has developed following recognition that the metal-carbon and metal-metal multiple bonds present in certain low-valent transition-metal complexes are reactive centers for the attachment of metal-ligand fragments. The products contain metal-metal bonds which may be homo- or heteronuclear in nature. If bridging carbon atoms are present, leading to dimetallacyclopropane or -cyclopropene structures, the organic groups (alkylidene or alkylidyne) have an extensive chemistry. The isolobal connection, developed by *Hoffmann* et al., relating the frontier orbitals of organic groups with those of metal-ligand fragments, has been crucial in guiding the preparative work.

1. Introduction

The growth of organometallic chemistry since the discovery of the cyclopentadienylmetal compounds has been one of the dominant forces in the development of our science. Preparative work leading to new compounds has provided the infrastructure of the field, but in many instances novel products have been synthesised serendipitously. This is not surprising given the variable electronic properties of the d- and f-elements, the remarkable variety of ligand bonding modes, and the kinetic and thermodynamic influences at work. The admission that we lack sufficient predictive power in this area of endeavour is a reaffirmation of the vitality of the research, and not a statement to deplore. The degree of randomness in preparative organometallic chemistry is, however, rapidly decreasing. This is a welcome trend, for which there are several explanations. In this article the thesis will be advanced that by taking into account similarities between the frontier orbitals of metal-ligand fragments and those of particular organic groups, it is often possible to devise logical syntheses of new compounds with metal-metal bonds. Metal cluster compounds represent an active area of research.

2. Early Work

In 1979 we first drew attention[1] to the ability of $Pt(PMe_3)_2$ groups to bond to chromium and to tungsten compounds containing metal-carbon double- or triple-bonds, in a manner long known for alkenes and alkynes (Scheme 1). It thus became evident that the $Cr(CO)_5$ and $W(CO)_2(\eta^5\text{-}C_5H_5)$ groups must have bonding properties similar to those of CH_2(carbene) and CH(carbyne), respectively.

Halpern[2] appears to have been the first to appreciate that certain inorganic and organic groups are electronically equivalent. He drew attention to similarities in the reactivity patterns of alkyl radicals and the pentacoordinate cobalt(II) species $Co(CN)_5^{3\ominus}$, and between carbenes and tetracoordinate d^8-metal complexes. Other seminal work demonstrating electronic equivalence, deserves mention. Through structural studies on $[As_3Co(CO)_3]$ and $[As_2Co_2(CO)_6]$, *Dahl*[3] pointed out the similarity in bonding modes of arsenic atoms and $Co(CO)_3$ groups in tetra-

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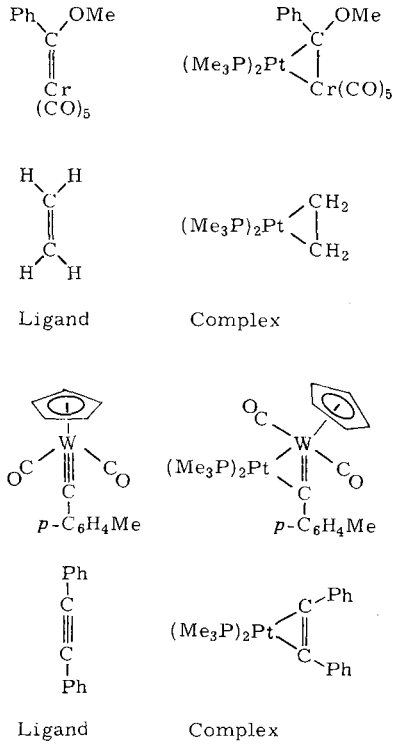


Scheme 1.

hedral clusters. *Hawthorne*[4] elegantly introduced the anion $C_2B_9H_{11}^{2\ominus}$ as a ligand in transition-metal chemistry, following an appreciation of its relationship to $C_5H_5^{\ominus}$. The discovery of the carbaboranes had previously established the equivalence of CH and $BH^{\ominus}$ groups[5,6]. Later, *Wade*[7] and *Mingos*[8] developed a skeletal electron-pair theory which related the structures of certain polynuclear carbonylmetal species with those of polyhedral borane anions, recognizing a similarity in the bonding properties of $Ru(CO)_3$ and BH groups.

3. Synthetic Strategies and The Isolobal Model

Organic chemists have long been accustomed to viewing the synthesis of a compound in terms of a series of one-step interconversions of suitable precursors. The synthetic strategy is conceived by first considering the nature of the organic groups present in the desired product, and then deciding, on the basis of experience, how these fragments may be assembled. In this context, the principle of conservation of orbital symmetry has recently proved to be an exceptionally powerful predictive tool[9]. Concerted reactions proceed readily when there is a similarity in the orbital symmetry properties of reactants and products. Consideration of the frontier orbitals of molecules provided the key to the development of the Woodward-Hoffmann rules.

Recently, *Hoffmann*[10] has elegantly employed frontier orbital similarities to relate the building blocks of hydrocarbon chemistry (CH_3, CH_2, CH, and C) with those of various metal-ligand combinations, thereby accounting for the existence of a range of organometallic complexes. For fragments derived from a metal in an octahedral environment, *Hoffmann* demonstrated the isolobal relationships:

$CH_3 \leftrightarrow Mn(CO)_5$
$CH_2 \leftrightarrow Fe(CO)_4$
$CH \leftrightarrow Co(CO)_3$

Groups are defined as isolobal if the number, symmetry properties, approximate energy and shape of their frontier orbitals, and the number of electrons they contain are similar[10,11]. A "two-headed arrow" with half an orbital below is the symbol used to indicate an isolobal connection.

The derivation by *Hoffmann* et al. of a library of molecular orbitals for metal-ligand fragments which serve as building blocks in organometallic chemistry has provided a sound basis for the correlations noted earlier. Thus, the CH_3 radical is isolobal with the ion $Co(CN)_5^{3\ominus}$ (Co^{II}, d^7), the CH_2 group is isolobal with the platinum fragments PtL_2 (Pt^0, d^{10}; L = PR_3 or CO; L_2 = cod = 1,5-cyclooctadiene), and CH is isolobal with $W(CO)_2(\eta^5\text{-}C_5H_5)$ (W^I, d^5) (Table 1 and Figure 1).

The isolobal analogy is useful in relating the structures of metal complexes with those of simple organic molecules. Compound **1**, for example, which was serendipitously prepared[12], may with hindsight be related structurally to spiro[2.2]pentane. This is because $Fe(CO)_4$ is isolobal with CH_2, and Sn with C. A further interesting comparison involves compounds **2** and **3**, both obtained from the unsaturated molecule $[Os_3(\mu\text{-}H)_2(CO)_{10}]$ by treatment with CH_2N_2[13] or $[Pt(C_2H_4)(PPh_3)_2]$[14], respectively. Compound **2** exists in solution in tautomeric equilibrium with $[Os_3(\mu$-

Table 1. Isolobal relationships [a, b].

CH_3	CH_2	CH
$Mn(CO)_5$	$Fe(CO)_4$	$Co(CO)_3$
$Fe(CO)_2(\eta^5\text{-}C_5H_5)$	$Rh(CO)(\eta^5\text{-}C_5Me_5)$	$Ni(\eta^5\text{-}C_5H_5)$
$Mo(CO)_3(\eta^5\text{-}C_5H_5)$	$Re(CO)_2(\eta^5\text{-}C_5H_5)$	$W(CO)_2(\eta^5\text{-}C_5H_5)$
	$Cr(CO)(NO)(\eta^5\text{-}C_5H_5)$	$[Mn(CO)_2(\eta^5\text{-}C_5H_5)]^{\oplus}$
$Co(CO)_4$	$Cr(CO)_5$	$Re(CO)_4$
$PtH(PPh_3)_2$ [c]	$Pt(PMe_3)_2$ [d]	
$Zn(\eta^5\text{-}C_5H_5)$	$Cu(\eta^5\text{-}C_5Me_5)$	$Rh(\eta^6\text{-}C_6H_6)$
$Au(PPh_3)$	$IrCl(CO)_2$	$Re(CO)_3Br_2$
$Rh(PPh_3)_2(\eta^5\text{-}C_2B_9H_{11})$	$Fe(CO)_2(\eta^5\text{-}C_2B_9H_{11})$	$Mn(CO)_2(\eta^5\text{-}C_2B_9H_{11})$
	$TaMe(\eta^5\text{-}C_5H_5)_2$	$TaCl(PMe_3)_2(\eta^5\text{-}C_5H_5)$
$CH_3^{\oplus}$	$CH_2^{\oplus}$	$CH^{\oplus}$
$Cr(CO)_5$	$Mn(CO)_4$	$Fe(CO)_3$
$Mn(CO)_2(\eta^5\text{-}C_5H_5)$	$Fe(CO)(\eta^5\text{-}C_5H_5)$	$Rh(\eta^5\text{-}C_5H_5)$
BH_3	BH_2	BH

[a] The list has been compiled to illustrate the chemistry described in the text and is by no means exhaustive. Moreover, it should be noted that the isolobal mapping is not a one-to-one relationship. Thus $Cr(CO)_5$ is isolobal with CH_2 or $CH_3^{\oplus}$ (cf. [10]). The frontier orbitals of the fragments listed are mostly derived by considering the metal to be in a six-coordinate octahedral environment. However, the model can be extended to seven-, eight- or nine-coordinate structures (Table 2); thus, for example, accounting for $Re(CO)_4 \leftrightarrow CH$ or $Mo(CO)_3(\eta^5\text{-}C_5H_5) \leftrightarrow CH_3$. [b] From Table 2 it can be seen that the isolobal property derives from the oxidation state of the metal and the number of ligands. It thus makes no difference whether in a PtL_2 group L is a monodenate ligand such as PMe_3, PPh_3 or CO, or if L_2 is a bidentate ligand such as cycloocta-1,5-diene. Similar considerations apply to anionic electron-pair donors; thus $Cl^{\ominus}$ and $Br^{\ominus}$, or $\eta^5\text{-}C_5H_5^{\ominus}$ and $\eta^5\text{-}C_5Me_5^{\ominus}$ are pairs of equivalent ligands as far as the isolobal connection is concerned. [c] This is an ML_3 (Pt^I, d^9) C_{2v} (T-shaped) fragment with one high-lying orbital, and is thus related to a ML_5 (Mn^0, d^7) fragment derived from an octahedron (cf. [10]). [d] The $Pt(PR_3)_3$ group is also isolobal with CH_2 (see Table 2); however, it is rarely found in complexes, in contrast to the ubiquitous $Pt(PR_3)_2$ fragment. The latter has two high-lying orbitals with two electrons, the remaining eight electrons of Pt^0 (d^{10}) filling the nonbonding d_{z^2} orbital and the t_{2g} set (cf. [10]). Thus $Pt(PR_3)_2$ groups play an important role in the extensive chemistry of platinum in which the metal 'has a 16 shell' or 'functions as a 16 electron species'.

$H)_2(\mu\text{-}CH_2)(CO)_{10}]$, and the latter is the only tautomer present in the solid state. Nevertheless, **2** with its agostic[15] hydrogen atom is well authenticated by NMR studies[13]. The relationship between **2** and **3** lies in the presence of the isolobal fragments CH_3 and $PtH(CO)(PPh_3)$ (ML_3, d^9, essentially C_{2v} symmetry or T-shaped).

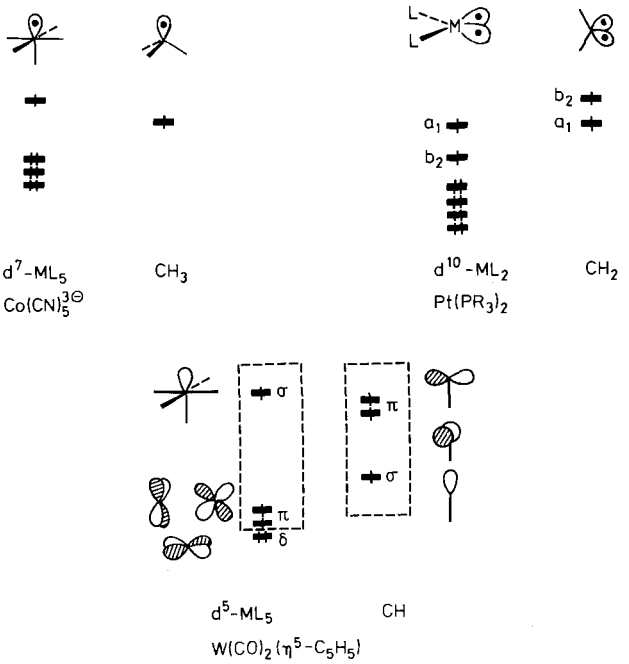
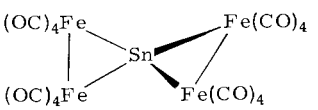


Fig. 1. Isolobal analogies between hydrocarbon and metal-ligand fragments.

Although the isolobal model[10] has hitherto been primarily used to recognize structural relationships between organometallic and organic molecules, it is now timely to consider its use as a predictive tool for the synthesis of novel compounds. Having conceived a desired molecule as comprising a collection of fragments, one can consider its synthesis via the assembly of appropriate groups, bearing in mind fragment molecular orbital similarities such as those shown in Table 1. The examples in Table 1 are by no



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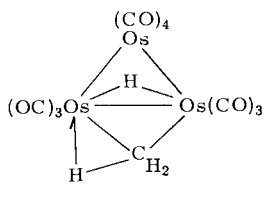

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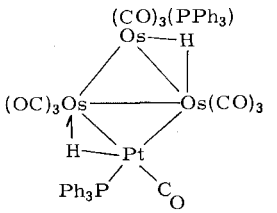

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means exhaustive and follow from conclusions drawn elsewhere[10], which have been usefully summarized by *Hoffmann* in the form shown in Table 2.

Before describing some planned synthesis of compounds with metal-metal bonds, it is necessary to point out that isolobal mapping between fragments does not necessarily lead to identical chemical behavior. For example, whereas CH_2 dimerizes to ethylene or polymerizes, the inorganic "methylene" groups $Pt(PR_3)_2$ do not follow this reactivity pattern. It is true that the diplatinum compound $[Pt_2\{tBu_2P(CH_2)_3PtBu_2\}_2]$ exists[16], which is a dimer of the $Pt(PR_3)_2$ species $Pt\{tBu_2P(CH_2)_3PtBu_2\}$, but the Pt_2P_4 core of the complex is not planar as is C_2H_4. Moreover, a Pt=Pt double bonded species would naturally be expected to have the configuration $(\sigma_d)^2(\sigma_d^*)^2(\pi_d)^2(\sigma)^2$; however, in $[Pt_2\{tBu_2P(CH_2)_3PtBu_2\}_2]$ the σ level does not lie below π_d^*, and the actual configuration is $(\sigma_d)^2(\sigma_d^*)^2(\pi_d)^2(\pi_d^*)^2$[17]. Formally, this leads to a zero Pt–Pt bond order, and thus a $Pt(PR_3)_2$ d^{10}-species would not be expected to dimerize[18,19]. Nevertheless, there are Pt–Pt bonding interactions in the diplatinum compound caused by s,p orbital mixing into σ_d and σ_d^* orbitals[17]. If the R groups are bulky, stable $Pt(PR_3)_2$ complexes are known, otherwise these species disproportionate to afford 16- or 18-electron $Pt(PR_3)_n$ (n=3 or 4) complexes and clusters with $Pt(PR_3)$ groups. Hence, a fragment such as $Pt(PMe_3)_2$ is best trapped as the complex $[Pt(C_2H_4)(PMe_3)_2]$, from which ethylene is readily released on treatment with various reagents.

Most of the inorganic species in Table 1 are not stable as dimers under normal conditions. Thus $[Fe_2(CO)_8]$ only exists at low temperatures in a rare gas matrix[20], since with CO it readily affords the thermodynamically more stable $[Fe_2(CO)_9]$. Dimeric forms of $Co(CO)_3$ and $Ni(\eta^5\text{-}C_5H_5)$, with formal metal-metal triple bonds, are also unstable. However, these fragments occur in the polynuclear compounds $[Co_4(CO)_{12}]$[21] and $[Ni_6(\eta^5\text{-}C_5H_5)_6]$[22]. In contrast, $[Rh_2(CO)_2(\eta^5\text{-}C_5Me_5)_2]$[23] and $[W_2(CO)_4(\eta^5\text{-}C_5H_5)_2]$[24] exist as formal analogues of ethylene and an alkyne, respectively. It may be concluded that isolobal metal-ligand fragments only combine with each other or with organic species in kinetically and thermodynamically favorable circumstances and, in combining, these same factors will determine the nature of the final product. Relative energy differences among the frontier orbitals will have a very important influence on the result.

Table 2. Isolobal analogies (after [10]).

Organic fragment	Coordination number of the transition metal on which the 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.

4. Trimetallacyclopropanes

A multitude of compounds with metal-metal bonds is known, and these often involve atoms of different elements[25]; both for homo- and heteropolynuclear metal complexes a triangular array of metal atoms is a common structural feature. Although in this article we focus on heteronuclear metal species, the homonuclear trirhodium an-

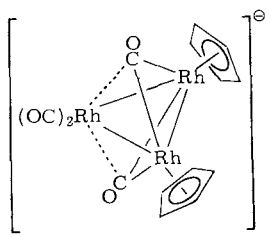
ion **4**[26] is important since its existence prompted development of a useful bonding model[27]. The fragment $Rh_2(\mu\text{-}CO)_2(\eta^5\text{-}C_5H_5)_2$ has frontier orbitals similar to those of ethylene. Moreover, because $Rh(CO)_2^{\ominus}$ is isolobal with CH_2, the anion **4** is properly described as a trimetallacyclopropane. This analogy is supported by the synthesis of the dimetallacyclopropane **5**[28,29].

It follows that if $[Rh_2(\mu\text{-}CO)_2(\eta^5\text{-}C_5H_5)_2]$, with a formal metal-metal double bond, is related to ethylene it should form adducts with a variety of metal-ligand fragments which are isolobal with methylene. The products would then be analogues of olefin-metal complexes. It is not possible to test this idea with $[Rh_2(\mu\text{-}CO)_2(\eta^5\text{-}C_5H_5)_2]$ since this compound has not been reported. However, the related complex $[Rh_2(\mu\text{-}CO)_2(\eta^5\text{-}C_5Me_5)_2]$ has fortunately been prepared[23], and we have focussed on its reactions with the fragments PtL_2 ($L=PR_3$, $L_2=$cod) and $M(CO)_5$ (M = Cr, Mo, W); these species are readily accessible from labile complexes containing a weakly bound ligand. Thus, the compounds $[Pt(C_2H_4)(PR_3)_2]$ and $[Pt(cod)_2]$ are sources of $Pt(PR_3)_2$ and Pt(cod), respectively[30]. The $M(CO)_5$ groups may be obtained by UV irradiation of the hexacarbonyls in tetrahydrofuran (THF) or acetonitrile, thereby producing the reactive complexes $[M(CO)_5(THF)]$ (M = Cr, W) and $[Mo(CO)_5(NCMe)]$[31].

As expected, $[Pt(cod)_2]$ reacts with $[Rh_2(\mu\text{-}CO)_2(\eta^5\text{-}C_5Me_5)_2]$ to afford **6**[32], whereas the $[M(CO)_5(ligand)]$ species give the compounds **7**[33]. However, treatment of $[Rh_2(\mu\text{-}CO)_2(\eta^5\text{-}C_5Me_5)_2]$ with $[Pt(C_2H_4)(PPh_3)_2]$ leads to a complex mixture. The major product **8** contains the fragment $Pt(CO)(PPh_3)$ which, although isolobal with CH_2, demonstrates that the reaction is not mechanistically simple, a frequent occurrence in organometallic chemistry.

Protonation of **8** with $HBF_4\cdot Et_2O$ gives the salt **9**[32]. The structure of the cation is of considerable interest in terms of the isolobal analogy, since it is a model for protonated cyclopropane[34]. Moreover, the cation contains a $PtH(CO)(PR_3)^{\oplus}$ group isolobal with $CH_3^{\oplus}$.

The syntheses leading to **6**—**8** can be extended in several ways. For example, *Dahl* et al.[35] have shown that photochemically generated metal fragments, isolobal with methylene, add to the unsaturated dicobalt compound $[Co_2(\mu\text{-}CO)_2(\eta^5\text{-}C_5Me_5)_2]$ to afford complexes such as, e.g., $[Co_2Mn(\mu_2\text{-}CO)_3(\mu_3\text{-}CO)(\eta^5\text{-}C_5H_4Me)(\eta^5\text{-}C_5Me_5)_2]$. Recently, the compound $[CoRh(\mu\text{-}CO)_2(\eta^5\text{-}C_5Me_5)_2]$ has been prepared from the reaction between $[Rh(CO)_2(\eta^5\text{-}C_5Me_5)]$ and $[Co(C_2H_4)_2(\eta^5\text{-}C_5Me_5)]$[36]. This heteronuclear dimetal complex reacts with several carbene-like inorganic fragments to give trimetallacyclopropanes which incorporate three different metallic elements, *e.g.* **10**—**12**.



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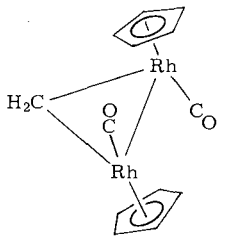

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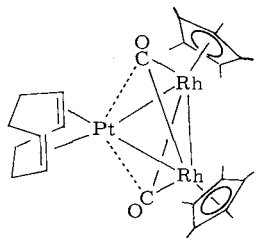

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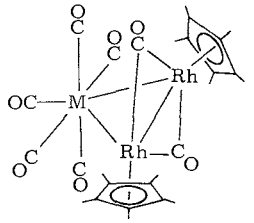
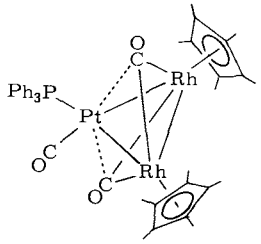


7a, M = Cr; **7b**, M = Mo; **7c**, M = W



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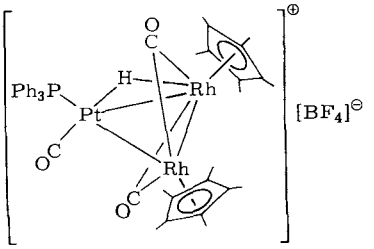

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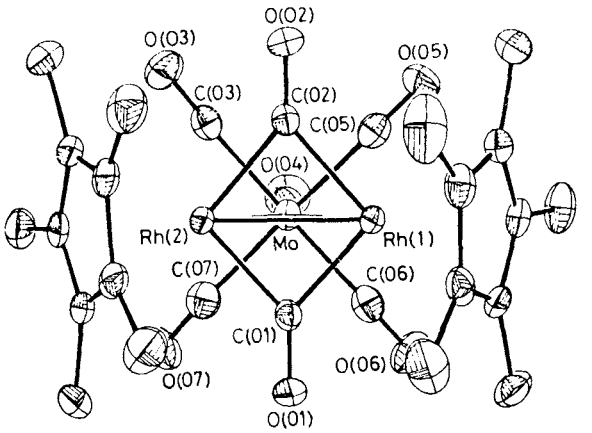
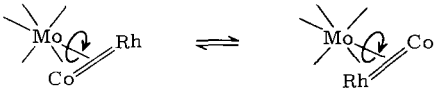


Fig. 2. The molecular structure of $[MoRh_2(\mu\text{-}CO)_2(CO)_5(\eta^5\text{-}C_5Me_5)_2]$ **7b** in the crystal [37].

Although it has not proved possible to grow crystals of **12** for X-ray structure analysis, this has been carried out for the closely related compound **7b**, whose structure is shown in Figure 2[37]. At room temperature, the $^{13}C\{^1H\}$-NMR spectra of **7b** and **12** both exhibit two signals for the $Mo(CO)_5$ group (relative intensity 4 : 1). For **12** this implies dynamic behavior involving rotation of the Co=Rh fragment about an axis through the Mo atom and the midpoint of the Co—Rh vector so that the CO sites of the *cis*-$Mo(CO)_4$ group are averaged on the NMR timescale:

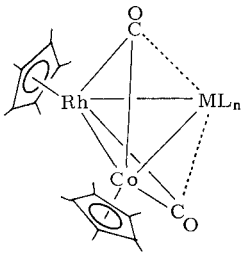


At −60 °C the limiting spectrum for **12** is observed, with the $Mo(CO)_5$ group giving rise to three resonances of relative intensity 2 : 2 : 1. From the coalescence temperature of *ca.* −15 °C, the barrier to rotation for the process is estimated[37] to be 52.3 ± 1.3 kJ mol^{-1}. This $\Delta G^{\neq}$ value lies in the range found for hindered rotation of alkenes in their

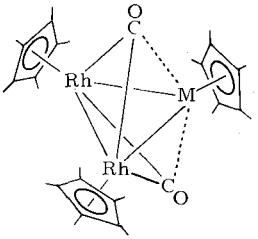
d^6-ML_5 complexes, thus strengthening the analogy between trimetallacyclopropanes such as **6**—**8** or **10**—**12** and $[M(C_2H_4)L_n]$ compounds.

Removal of a proton from **5** would formally yield the cationic methylidyne complex $[Rh_2(\mu\text{-}CH)(CO)_2(\eta^5\text{-}C_5H_5)_2]^{\oplus}$. Although this species is not known, the analogues **13** have been prepared[36] by treating $[Rh_2(\mu\text{-}CO)_2(\eta^5\text{-}C_5Me_5)_2]$ with $[M(C_2H_4)_2(\eta^5\text{-}C_5Me_5)]$ (M = Co, Rh). The latter are sources of $M(\eta^5\text{-}C_5Me_5)$, which are isolobal with $CH^{\oplus}$. The molecular structure of **13b** established by X-ray structure analysis[38] involves CO ligands which are semitriply bridging, as predicted by theoretical considerations[27].

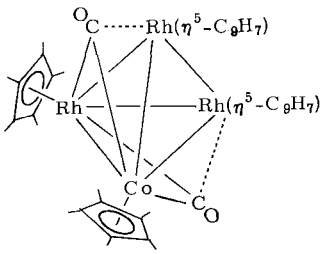
The fragment $Rh(\eta^5\text{-indenyl})$ is isolobal with $Rh(\eta^5\text{-}C_5Me_5)$. However, reaction of $[CoRh(\mu\text{-}CO)_2(\eta^5\text{-}C_5Me_5)_2]$ with $[Rh(C_2H_4)_2(\eta^5\text{-}C_9H_7)]$ affords the tetranuclear complex **14**, rather than an unsaturated trimetal compound $[CoRh_2(\mu\text{-}CO)_2(\eta^5\text{-}C_9H_7)(\eta^5\text{-}C_5Me_5)_2]$, similar to **13**. This again serves as a caveat that the isolobal model has its limitations when used to predict the final product of a chemical reaction. Nevertheless, if it is borne in mind that the steric effect of ligands or other factors will govern the course of the reaction, either inhibiting it altogether or leading to a thermodynamically more stable product, synthetic strategies based on isolobal connections can be valuable. A further example should illustrate these points. The $[Rh_2(\mu\text{-}CO)_2(\eta^5\text{-}C_5Me_5)_2]$/ethylene mapping, coupled with the existence of $[Pt(C_2H_4)_3]$ with its easily displaced ethylene ligands, suggested a reaction between the dirhodium compound and tris(ethylene)platinum. Loss of some or all of the ethylene groups should occur to form a rhodium-platinum cluster compound. However, because of the steric requirements of the bulky $\eta^5\text{-}C_5Me_5$ ligands it was believed that a $PtRh_6$ core structure would probably not be formed. In fact, complex **15**, in which all C_2H_4 groups are displaced[39], was produced in virtually quantitative yield.



10, ML_n = Pt(cod)
11, ML_n = $Fe(CO)_4$
12, ML_n = $Mo(CO)_5$



13a, M = Co
13b, M = Rh



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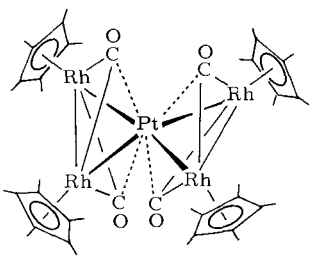


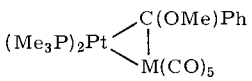
15

Formally, **15** is related to the bulky $Pt(PR_3)_2$ complexes mentioned earlier, but equally well an isolobal correlation could have been made if the product had been $[Pt(C_2H_4)\{Rh_2(CO)_2(\eta^5\text{-}C_5Me_5)_2\}_2]$, analogous to $[Pt(C_2H_4)(PR_3)_2]$.

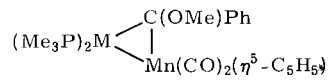
Once the structure of the pentametallaspiro[2.2]pentane **15** had been established, the synthesis of several related species became clear. For example, since Au^I is isoelectronic with Pt^0, the compound $[AuRh_4(\mu\text{-}CO)_4(\eta^5\text{-}C_5Me_5)_4][PF_6]$ was prepared by treating a mixture of $[Rh_2(\mu\text{-}CO)_2(\eta^5\text{-}C_5Me_5)_2]$ and $TlPF_6$ with [AuCl(tht)] (tht = tetrahydrothiophene)[40].

5. Dimetallacyclopropanes

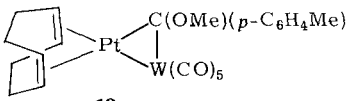
Compounds of type **16** are dimetallacyclopropanes and are readily prepared[41] by using the Fischer[42] carbene compounds $[(OC)_5M{=}C(OMe)Ph]$ (M = Cr, Mo, W) as ligands to displace ethylene from $[Pt(C_2H_4)(PMe_3)_2]$. The $Cr(CO)_5$ fragment is isolobal with CH_2, and since the $Mn(CO)_2(\eta^5\text{-}C_5H_5)$ group is also an ML_5 (d^6) species (Table 2), the syntheses of compounds **17** thus logically followed those of **16**[43].



16a, M = Cr
16b, M = Mo
16c, M = W



17a, M = Pt
17b, M = Pd
17c, M = Ni



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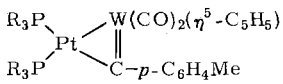
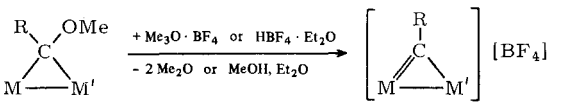


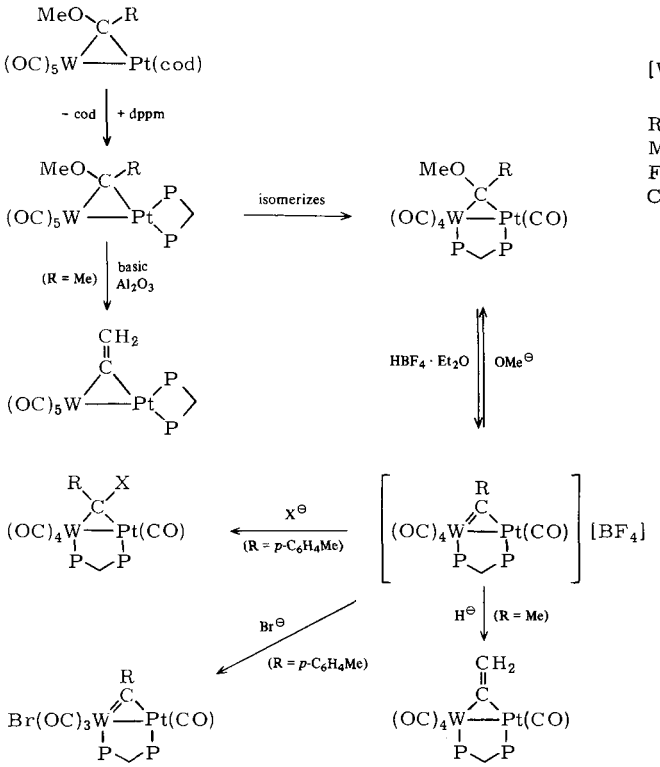
19a, PR_3 = PMe_2Ph
19b, PR_3 = PMe_3

The alkylidene groups in **16** and **17** and in related compounds do not symmetrically bridge the metal-metal bonds. In complex **16c** the μ-C—Pt [2.04(1) Å] and μ-C—W [2.48(1) Å] distances are so disparate that this compound can be viewed as involving a $W(CO)_5$ group coordinated to a $Ph(MeO)C{=}Pt(PMe_3)_2$ moiety. The asymmetry is also reflected in the chemical behavior. Thus, when **16a** is refluxed in toluene it decomposes to afford the triplatinum compounds $[Pt_3\{\mu\text{-}C(OMe)Ph\}_2(\mu\text{-}CO)(PMe_3)_3]$ and $[Pt_3\{\mu\text{-}C(OMe)Ph\}_3(PMe_3)_3]$[41]. Carbene transfer from one metal center to the other also occurs in the reaction of **18** with CO to yield $[Pt_3\{\mu\text{-}C(OMe)R\}_3(CO)_3]$ (R = p-C_6H_4Me)[44].

For compounds containing the μ-C(OMe)R ligand, an important reaction is the removal of the OMe group by methylation or protonation:



The cationic bridged alkylidyne species produced have an extensive chemistry. However, undesired side reactions in-

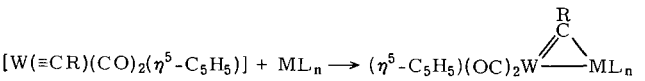


Scheme 2. R = Me, *p*-C_6H_4Me; dppm = $Ph_2PCH_2PPh_2$; X = H, Me, S-*p*-C_6H_4Me.

volving cleavage of the metal-metal bonds and migration of the carbene ligands must not occur. This pathway may be blocked by supporting the metal-metal bond with a bidentate ligand, as illustrated in Scheme 2[45].

6. Dimetallacyclopropenes

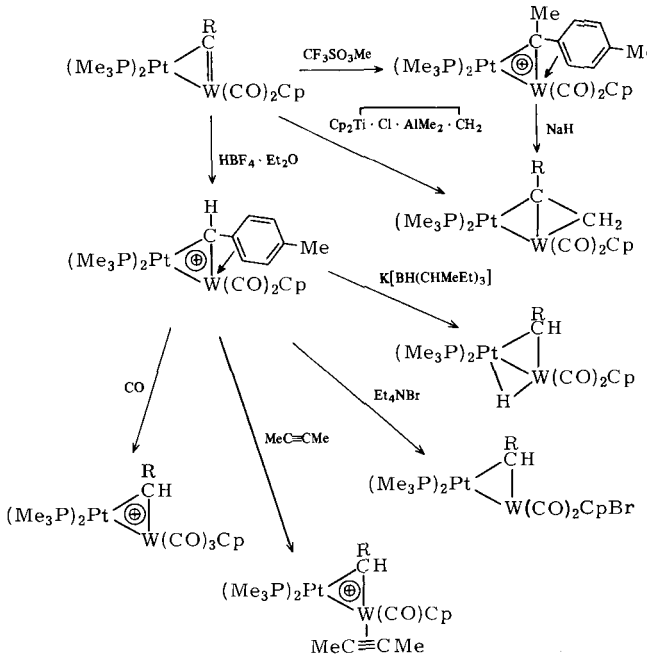
Reference was made earlier to the analogy between the frontier orbitals of CR and $W(CO)_2(\eta^5\text{-}C_5H_5)$ (Scheme 1), first recognized[1,46] in the formation of **19a** by displacement of ethylene from $[Pt(C_2H_4)(PMe_2Ph)_2]$ with



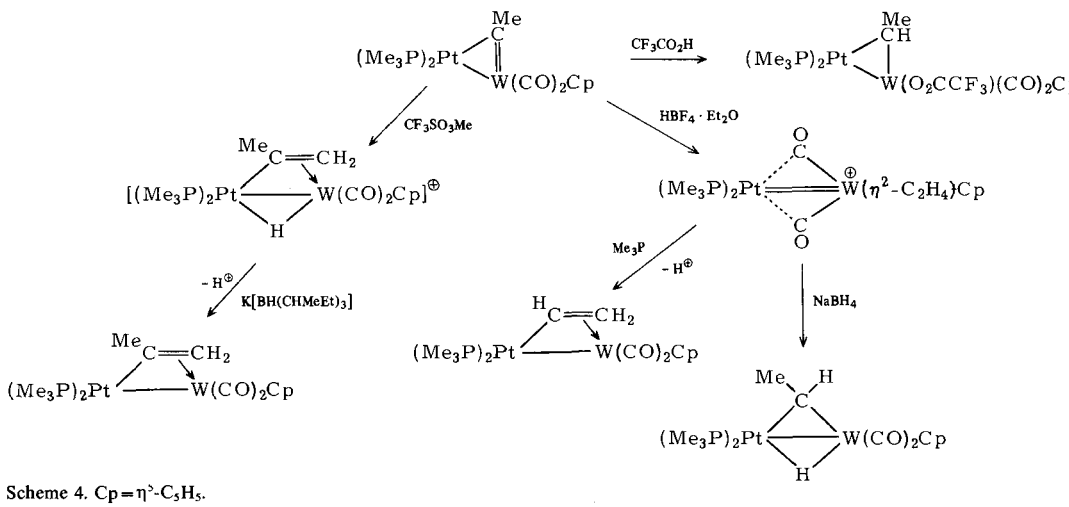
R = *p*-C_6H_4Me; ML_n = $Pt(PR_3)_2$, $M(CO)(\eta^5\text{-}C_5Me_5)$ (M = Co, Rh), $M(CO)(\eta^5\text{-}C_9H_7)$ (M = Rh, Ir), M(CO)(acac) (M = Rh, Ir), $Fe(CO)_4$, $Mn(CO)_2(\eta^5\text{-}C_5H_4Me)$, $Re(CO)_2(\eta^5\text{-}C_5H_5)$, $Cr(CO)_2(\eta^6\text{-}C_6Me_6)$ $Cr(CO)(NO)(\eta^5\text{-}C_5H_5)$, $M(\eta^2\text{-}CO)(\eta^5\text{-}C_5H_5)_2$ (M = Ti, Zr)

$[W(\equiv CC_6H_4Me\text{-}4)(CO)_2(\eta^5\text{-}C_5H_5)]$. An X-ray structure analysis of **19a** showed that the μ-C–W distance (1.967(6) Å) corresponds to that expected for a double bond, and hence the description of the three-membered ring as a dimetallacyclopropene is appropriate.

The reaction which afforded **19a** is remarkably general. A range of metal-ligand fragments isolobal with CH_2 readily form 1:1 adducts with $[W(\equiv CC_6H_4Me\text{-}4)(CO)_2(\eta^5\text{-}C_5H_5)]$[47].



Scheme 3. Cp = η^5-C_5H_5, R = *p*-C_6H_4Me.



Scheme 4. Cp = η^5-C_5H_5.

X-Ray structure analysis of several of the bimetal compounds reveal μ-C–W distances which support the dimetallacyclopropene formulation. The synthesis is the most systematic yet devised for preparing complexes with metal-metal bonds between tungsten and another transition metal. The scope of the reaction remains to be established by further experiments. So far, it is known that the R substituent may be alkyl rather than aryl, and it is likely that similar reactions will occur with the chromium and molybdenum derivatives $[M(\equiv CR)(CO)_2(\eta^5\text{-}C_5H_5)]$ (M = Cr, Mo). Whether carbyne complexes of earlier transition metals, such as tantalum, will behave as ligands in a manner similar to $[W(\equiv CR)(CO)_2(\eta^5\text{-}C_5H_5)]$ has yet to be determined. The C≡Os group in the osmium complex $[OsCl(\equiv CC_6H_4Me\text{-}4)(CO)(PPh_3)_2]$ is known to add to copper, silver, and gold centers[48].

Dimetallacyclopropenes containing tungsten may be used as precursors for the synthesis of metal cluster compounds (cf. Section 8); however, interest also focuses on the reactivity of the bridging μ-CR groups. To date, attention has been directed mainly at the tungsten-platinum species, and some of their reactions are outlined in Schemes 3 and 4[49–51]. The very different character of the products obtained with $HBF_4 \cdot Et_2O$, depending on the nature of the μ-CR group (R = *p*-C_6H_4Me or Me), should be noted.

7. Copper, Silver, and Gold

Many cluster compounds containing $Au(PPh_3)$ groups are known, and from structural studies it has been widely appreciated that these groups are isolobal with H or CH_3 since all three species have a frontier orbital containing a single electron[52–54]. Although this analogy recedes in species with two or more $Au(PPh_3)$ groups[55], it remains useful in devising syntheses of compounds containing a single Au atom.

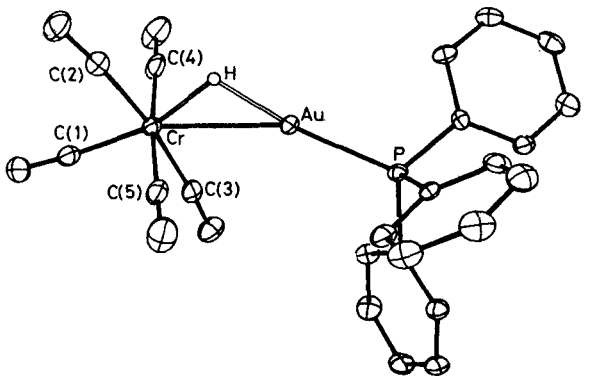


Fig. 3. The molecular structure of $[AuCr(\mu\text{-}H)(CO)_5(PPh_3)]$ in the crystal [60].

The hydrido-bridged anions $[M_2(\mu\text{-}H)(CO)_{10}]^{\ominus}$ (M = Cr, Mo, W) were seminal compounds[56–59] in modern inorganic chemistry since their electron deficient three-center two-electron bridge systems provided a key link between transition-metal chemistry and that of the boranes, for which such bridge-bonding by hydrogen had long been known.

The dichromium anion $[Cr_2(\mu\text{-}H)(CO)_{10}]^{\ominus}$ can be considered to be a combination of the two fragments $CrH(CO)_5^{\ominus}$ and $Cr(CO)_5$, the former fragment behaving as an electron-pair donor and the latter as an electron-pair acceptor, isolobal with $CH_3^{\oplus}$ (Table 1). Because of the isolobal relationship $CH_3^{\oplus} \leftarrow\!\!\circ\!\!\rightarrow [Au(PPh_3)]^{\oplus}$, it follows that the neutral complex $[AuCr(\mu\text{-}H)(CO)_5(PPh_3)]$ might exist, given favorable thermodynamic factors. The desired compound (Fig. 3) has been obtained from the reaction of $[N(PPh_3)_2][CrH(CO)_5]$ and $[AuCl(PPh_3)]$ in tetrahydrofuran[60]. Because of the isolobal relationships $Cr(CO)_5 \leftarrow\!\!\circ\!\!\rightarrow M(CO)_6$ (M = Mo or W), and $Au(PPh_3) \leftarrow\!\!\circ\!\!\rightarrow Ag(PMe_3)$, the related compounds

$[MM'(\mu\text{-}H)(CO)_5(PR_3)]$

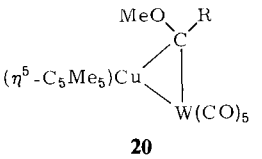
M	M′	R
Mo	Au	Ph
W	Au	Ph
Cr	Ag	Me
W	Ag	Me

have been synthesized by a similar route.

Although several cluster compounds incorporating a copper atom in the framework have been described[25], a reagent capable of supplying a copper moiety in a fragment isolobal with CH_2 or CH could be useful in synthesis. Since $Ni(\eta^5\text{-}C_5H_5)$ (ML_3, d^9) is isolobal with CH, the following relationships hold

$Cu(\eta^5\text{-}C_5H_5)$ (ML_3, d^{10}) $\leftarrow\!\!\circ\!\!\rightarrow CH_2$
$Zn(\eta^5\text{-}C_5H_5)$ (ML_3, $d^{10}\,s^1$) $\leftarrow\!\!\circ\!\!\rightarrow CH_3$

Taking into account that complexes containing $M(\eta^5\text{-}C_5Me_5)$ groups are sometimes more stable than those con-



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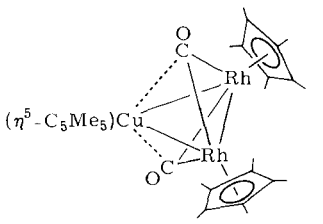

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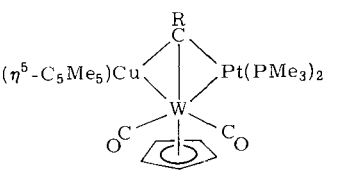

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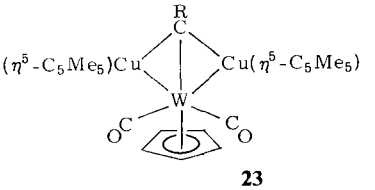
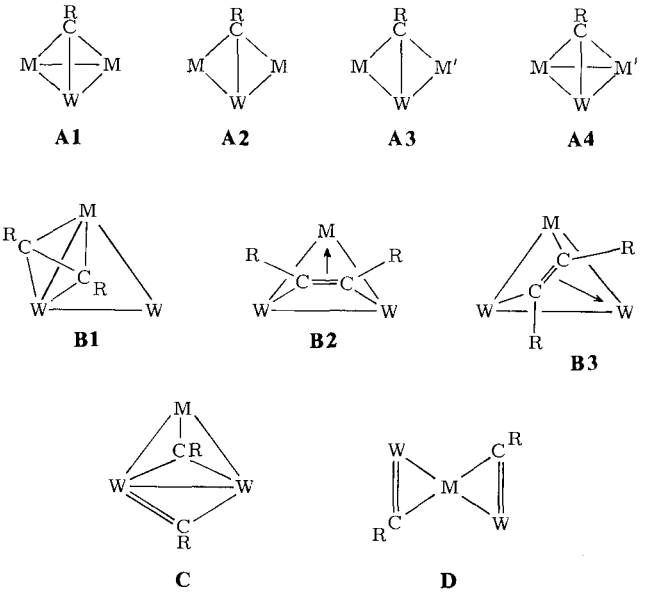


23

taining M(η-C_5H_5), treatment of CuCl with LiC_5Me_5 in tetrahydrofuran affords a reagent which is a ready source of the Cu(η⁵-C_5Me_5) fragment[61]. The latter adds to the unsaturated complexes [W{=C(OMe)R}$(CO)_5$], [Rh_2(μ-CO)$_2$(η⁵-$C_5Me_5)_2$], and [PtW(μ-CR)$(CO)_2(PMe_3)_2$(η⁵-C_5H_5)] to give compounds **20** to **22** (R = *p*-C_6H_4Me).

The analogy between the structure of **22** and that of the CH_2 adduct of [PtW(μ-CR)$(CO)_2(PMe_3)_2$(η⁵-C_5H_5)] depicted in Scheme 3 should be noted.

Interestingly, the reaction between [Cu(η⁵-C_5Me_5)(THF)] and [W(≡CR)$(CO)_2$(η⁵-C_5H_5)] affords the dicopper compound **23** (R = *p*-C_6H_4Me). This should be contrasted with the addition of $Pt(PR_3)_2$ fragments to [W(≡CR)$(CO)_2$(η⁵-C_5H_5)] to give the monoplatinum complexes [PtW(μ-CR)$(CO)_2(PR_3)_2$(η⁵-C_5H_5)][62]. Thus, although Cu(η⁵-C_5Me_5) and $Pt(PR_3)_2$ are isolobal, they show different reactivity patterns towards [W(≡CR)$(CO)_2$(η⁵-C_5H_5)], further illustrating that metal-ligand fragment analogies cannot be applied with certainty in synthesis, although their value as a guide-line in preparative work should be obvious.



Scheme 5. Core structures of trimetal compounds derived from [W(≡CR)$(CO)_2$(η⁵-C_5H_5)]. W = W$(CO)_2$(η⁵-C_5H_5), ligands on M and M′ are omitted for clarity. **A1**: M = Mo, W, Fe, Co, Rh, Ni; **A2**: M = Cu, Pt; **A3**: M = Cu, M′ = Pt; **A4**: M = Fe, M′ = Co, Rh, Pt; **B1**: M = Fe; **B2** and **B3**: M = Ru, Os; **C**: M = Re; **D**: M = Ni, Pd, Pt.

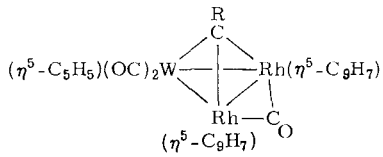
8. Metal-Clusters and -Chains

The dimetallacyclopropenes [MW(μ-CR)$(CO)_2(L_n)$(η⁵-C_5H_5)] (R = *p*-C_6H_4Me) discussed in Section 6 can serve as key building blocks for the synthesis of cluster complexes containing three or more metal atoms[63]. Reactions occur with metal-ligand fragments isolobal with CH_2, CH, or $CH^{\oplus}$ to afford products having a triangle of metal atoms capped by a CR group. Core structures observed for these clusters are of types **A1**—**A4** (Scheme 5). In addition to tungsten these clusters contain either two metal atoms of the same element or two metal atoms of different elements. Moreover, the core structures can be either closed (tetrahedrane) or "butterfly" (bicyclobutane).

A range of trimetal compounds of type **A** have now been prepared via designed syntheses, and a few examples will suffice to illustrate the approach. The synthesis of compounds **22** and **23**, species with core structures **A3** and **A2**, respectively is described in Section 7.

The binuclear complex [RhW(μ-CR)$(CO)_3$(η⁵-C_5H_5)(η⁵-C_9H_7)] affords **24** when treated with [Rh$(CO)_2$(η⁵-C_9H_7)]. Carbon monoxide is readily released in this reaction, and formally a Rh(η⁵-indenyl)(⟵O⟶CH) fragment has been added to the bimetal complex. The core structure of **24** corresponds to type **A1** (Scheme 5). Addition of an $Fe(CO)_3$ fragment (⟵O⟶$CH^{\oplus}$) to [RhW(μ-CR)$(CO)_3$(η⁵-C_5H_5)(η⁵-C_9H_7)] gives **25**[64], a species which is representative of structure type **A4**. Interestingly, this cluster contains atoms from the 3d-, 4d- and 5d-transition-metal series.

Several clusters of type **A1** have been prepared directly from [W(≡CR)$(CO)_2$(η⁵-C_5H_5)] (R = *p*-C_6H_4Me) and homonuclear dimetal compounds. Thus, the tolylmethylidynetungsten complex reacts with [$Co_2(CO)_8$] to give **26** in essentially quantitative yield[65]. An analogous reaction occurs with [$Mo_2(CO)_4$(η⁵-$C_5H_5)_2$] to afford **27**. The synthesis of **26** and **27** follows directly using the isolobal model as a guide. Both [$Co_2(CO)_8$] and [$Mo_2(CO)_4$(η⁵-$C_5H_5)_2$] were known to add alkynes readily to afford complexes [Co_2(μ-alkyne)$(CO)_6$] and [Mo_2(μ-alkyne)$(CO)_4$(η⁵-$C_5H_5)_2$], which are structurally analogous to **26** and **27**, respectively. However, the formation of **26** and **27**, and also that of the alkyne-bridged complexes, probably proceeds through the



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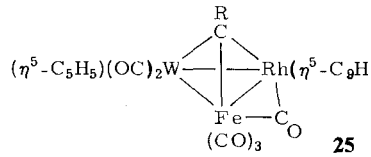

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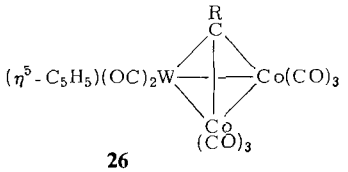
intermediacy of dimetal species which subsequently add $Co(CO)_3$ or $Mo(CO)_2$(η⁵-C_5H_5) fragments[65].

The dimetallacyclopropenes [MW(μ-CR)$(CO)_2(L_n)$(η⁵-C_5H_5)] also react with [W(≡CR)$(CO)_2$(η⁵-C_5H_5)] to give structures of type **B** (Scheme 5), which result from carbyne-coupling. The alkyne ligand thus formed may face- or edge-bridge the metal triangle, as found in species derived from iron, ruthenium, or osmium carbonyls[66].

As yet only one example is known of a compound with a core structure of type **C**—the rhenium compound **28** prepared by heating [W(≡CR)$(CO)_2$(η⁵-C_5H_5)] and [$ReBr(CO)_3(NCMe)_2$] in hexane[67]. The acetonitrile complex is a source of $ReBr(CO)_3$, a d^6-ML_4 fragment isolobal with $CH_2^{2\oplus}$ and $CH^{\oplus}$. Hence **28** has 46 cluster valence electrons rather than the customary 48 for a trimetal cluster in which all the metal atoms have 18-electron configurations. The core structure **C** is of considerable interest,



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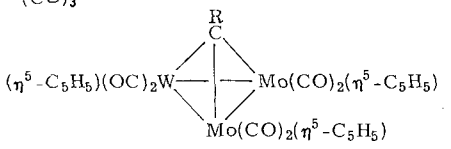

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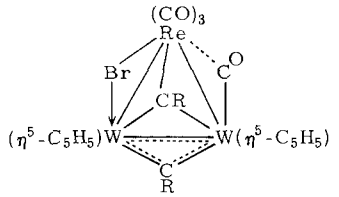

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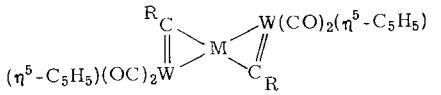
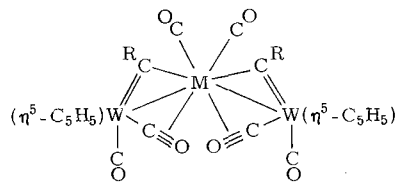


29a, M = Pt; **29b**, M = Pd; **29c**, M = Ni
29d, M = $Au^{\oplus}$; **29e**, M = $Ag^{\oplus}$



30a, M = Mo; **30b**, M = W

since it would appear to represent an intermediate on a pathway to type **B**.

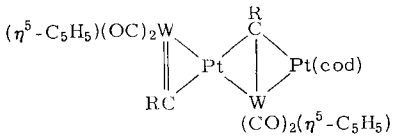
Structures of type **D** were first obtained from reactions between $[W(\equiv CR)(CO)_2(\eta^5\text{-}C_5H_5)]$ (R = *p*-C_6H_4Me) and labile olefin complexes of nickel, palladium, or platinum[68]. Thus $[Pt(C_2H_4)_3]$ afforded **29a** having a *pseudo*-tetrahedral structure. The angle between the two dimetallacyclopropene rings is 83°, and the metal spine is not linear (∢W–Pt–W 165°); however, in **29c** the W–Ni–W angle is 175°. Formation of **29a** parallels the synthesis of a family of $[Pt(alkyne)_2]$ complexes from reactions between $[Pt(C_2H_4)_3]$ and alkynes[69], providing another example of the successful use of the isolobal guide line in preparative work.

Having identified that the complexes **29** possess core structures of type **D** (Scheme 5), we can consider the preparation of related compounds. It is possible that the carbyne-tungsten ligands in **29a** function as four-electron donors to platinum, just as alkynes contribute four electrons to a metal center in certain complexes. In **29** there is some evidence for this in the presence and disposition of two semi-bridging CO ligands[68]. Assuming an 18-electron configuration for platinum in **29a**, albeit without proof, one can consider an isolobal mapping

$$Pt^0\,(d^{10}) \leftarrow\!\!\sigma\!\!- C^{4\oplus} \leftarrow\!\!\sigma\!\!- ML_2\,(d^6)$$

with all three species requiring 8 electrons for a filled shell. This prompted synthesis of the compounds **30** from $[W(\equiv CR)(CO)_2(\eta^5\text{-}C_5H_5)]$ and $[M(CO)_3(NCMe)_3]$ (M = Mo, W)[70]. These structures are interesting in two respects. First, the presence of *cis*-$M(CO)_2$ groups necessitates bent W–M–W spines (for **30a**, ∢W–Mo–W = 148°). Second, the complexes contain σ,η^2-CO ligands, and hence the central metal atom (Mo or W) acquires an 18 electron shell without the C≡W ligands functioning as four electron donors.

Since Au^I and Pt^0, as well as Ag^I and Pd^0 are isoelectronic pairs, it seemed likely that the cations **29d** and **29e** should exist. These species have been prepared as their $PF_6^{\ominus}$ and $BF_4^{\ominus}$ salts, respectively. Thus treatment of $[W(\equiv CR)(CO)_2(\eta^5\text{-}C_5H_5)]$ with [AuCl(tht)] in the presence of $TlPF_6$ gives **29d**, whereas $[Ag(NCMe)_4][BF_4]$ affords the silver compound **29e**[70b,71]. This readily releases $[W(\equiv CR)(CO)_2(\eta^5\text{-}C_5H_5)]$ in solution, and is less stable in this respect than the gold compound **29d**. In contrast, **29a** is sufficiently robust to be used with some success as a building block in the syntheses of compounds containing a chain of metal atoms, as described below.



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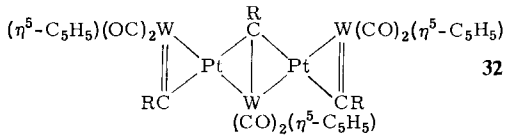

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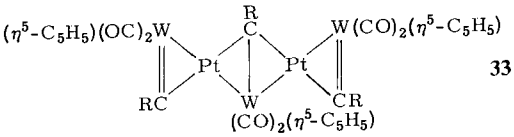

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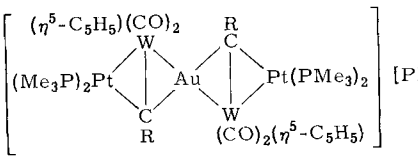

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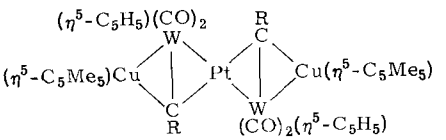

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Treatment of **29a** with $[Pt(cod)_2]$ results in the stepwise formation of compounds **31** and **32**. Reaction between **31** and one equivalent of $[W(\equiv CR)(CO)_2(\eta^5\text{-}C_5H_5)]$ gives the diplatinumtritungsten compound **33**[71]. The longest metal atom chain made so far in this way contains seven metal atoms with a Pt_3W_4 spine. This compound was prepared from **29a** and $[Pt(C_2H_4)_3]$. In principle, it should be possible to prepare oligomeric or polymeric Pt-W complexes,

but there are experimental difficulties. These include the observation that the chains tend to break to give mixtures of compounds with fewer metal atoms. Variation of the nature of the substituent R group may go some way to inhibit this tendency. Since the chain structures are not planar, the species exist in various conformations, increasing in complexity with chain length, and therefore making spectroscopic characterization very difficult. X-Ray crystallographic studies are crucial whenever single-crystals can be grown.

Nevertheless, despite the obvious difficulties, this is a promising area for research where considerations based on the isolobal model can be helpful. Thus Au^I may be substituted for Pt^0, and $Cu(\eta^5\text{-}C_5Me_5)$ for Pt(cod) or $Pt(PMe_3)_2$. For example, the gold compound **34** has been prepared by treating **19b** with [AuCl(tht)] in the presence of $TlPF_6$, and the copper complex **35** has been synthesized by addition of $[Cu(\eta^5\text{-}C_5Me_5)\cdot THF]$ to **29a**.

9. Conclusion and Outlook

As already stressed by *Hoffmann*[10], predictions based on isolobal analogies are bound to fail from time to time. At various places in this article attention has been drawn to this. Nevertheless, I hope to have demonstrated the value of the isolobal connection for synthesis in organometallic chemistry. Given that countless metal-ligand fragments are available to chemists via complexes containing labile groups (e.g. C_2H_4, THF, NCMe, N_2, etc.), it is possible to define a synthetic objective and the method of attaining it. It then remains to test the preparative pathway experimentally. As a creative area, organometallic synthesis has unlimited horizons!

I am indebted to Professor Roald Hoffmann for helpful discussions, and I thank Dr. Ward Robinson and Gregory Elliott for helpful comments. It will be evident that the work described depended much on stimulating collaboration with X-ray crystallographers, and I am indebted in this respect to Drs. Judith Howard, Guy Orpen, and Peter Woodward. Finally none of the work would have been possible without the able assistance of my co-workers listed in the relevant references.

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Routes to Functional Vesicle Membranes without Proteins

By Jürgen-Hinrich Fuhrhop* and Joachim Mathieu

Fixation of reaction partners at appropriate distances from one another is a structural prerequisite for vectorial reactions and reaction sequences. In biological systems (e.g. the photosynthetically active thylakoid membrane or membrane receptors) the positions of the reaction centers are fixed by membrane-protein complexes, but little is known about the structure of these complexes. Ordered reactive systems in synthetic vesicle membranes were first obtained by employing amphiphiles with reactive head groups as building units, by regioselective incorporation of foreign molecules into the membrane, by alignment of bolaamphiphiles with two head groups of differing solubility or size, and by the formation of domains. Chiral superstructures have also been observed in membranes, and the first stereoselective reactions have been performed in vesicle membranes. The report concludes with a brief discussion of membranes constructed from non-amphiphilic building blocks and problems which still have to be solved.

1. Introduction

Vesicles (lat. vesicula) are sealed, extremely thin (≤ 10 nm), often spherical membranes which enclose aqueous volumes of approximately 1 - 1000 μm^3. Synthetic vesicles formed by aggregation of a single amphiphile can be regarded as extremely simple models of highly organized, multifunctional biological cells[1,2]; for about seven years attempts have been made to equip these structures with properties analogous to those of a single cell. This review describes novel, reactive vesicles without proteins which have been used to try to simulate or modify the individual structural and dynamic properties of biological cells.

As an introduction, the structural units of biological membranes will be briefly dealt with, and their interactions and modes of functioning will be illustrated with the aid of two models. It is shown that the interesting characteristics of membrane reactions (vectorial, selective, rapid) can be accounted for by observable membrane properties which are, however, still not understood. The preparation and properties of protein-free vesicles from phospholipids is then described very briefly to bring in the topic of "synthetic vesicles". In the main part of this report we will only refer to those properties of synthetic vesicles which are not shared by phospholipid vesicles.

Biological cell membranes consist of a molecular bilayer (bilayer lipid membrane, BLM) of lipids (phospholipids, glycolipids) and proteins. According to the currently valid "fluid mosaic" model of *Singer* and *Nicolson*[3] (cf. Fig. 1a), the lipids form a matrix of liquid and liquid crystalline areas whose hydrophobic centers are spanned by proteins ("integral proteins"). Proteins which are associated with the hydrophilic head groups ("peripheral proteins") can be reversibly detached from the cell membrane (e.g. by changing the pH value). Integral proteins can only be isolated from the membrane with retention of their biological activity by using suitable detergents; the membrane is destroyed in the process. Furthermore, integral proteins in the membrane are not, or are only partially, attacked by water-soluble reagents (e.g. hydrolases), whereas peripheral proteins are accessible to these agents. The entire hydrophobic lipid and protein components form a phase which is sharply separated from water, although the distance from the aqueous environment only amounts to a few Ångstroms. Oligosaccharide chains of integral glycoproteins are often found on the outer cell surface and are responsible for (stereo-)selective interactions with substances dissolved in water. Selective interactions also take place between the proteins and the lipid matrix; predominantly negatively charged phospholipids (e.g. phosphatidyl serine) are, for example, closely bound to membrane proteins and form "domains" in the electroneutral phospholipid membranes (see Fig. 1).

The functions of biological membranes correspond with the living processes that occur in the cells: conversion of solar energy into chemical energy (photosynthesis), selective uptake of natural compounds (uptake of nutrients), production of electrical potentials and impulses (nerve excitation, movement), exchange of information with the environment (receptor action), etc. The course of biological reactions at membranes will be illustrated by two models: 1) the receptor action of chiral membrane surfaces and 2) light-induced charge separation at symmetrical membranes.

1) The "fluid mosaic" model for the reaction of a membrane receptor with a peptide hormone (Figs. 1a, b) demonstrates the relative sizes and mobility of the membrane building blocks[3]. Figure 1a shows the BLM with a lipid domain surrounding three integral glycoproteins and a peripheral protein molecule. The oligosaccharide and protein chains on the outer membrane surface are long, flexible arms which can pick up substances dissolved in water. These "arms" are composed of many chiral structures and form the highly specific binding center of the receptor. Association of the signal molecule (membrane ligand) with the receptor (Fig. 1b) changes the positions of the receptor proteins and their tertiary structures. The "signal" is thus conducted through the membrane by the integral proteins

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("allosteric effect") and can then trigger off subsequent reactions at the inner surface (e.g. aggregation of actin units to form fibrils).

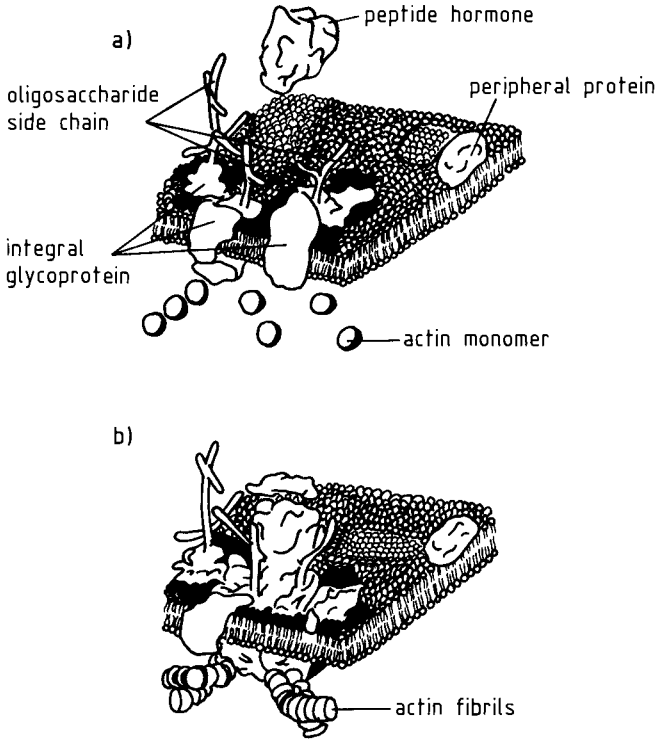


Fig. 1. a) "Fluid mosaic" model of a membrane receptor.—b) Attachment of a peptide hormone (="signal molecule") results in rearrangement of the receptor proteins within a "domain" of the membrane. This triggers subsequent reactions inside the cell (in this case the aggregation of actin molecules). The molecular interactions between the signal molecule and the receptor protein, those within the receptor-protein complex, and also those between the receptor protein and the actin units have not yet been elucidated in detail [3b].

2) The schematic model for the light-induced cleavage of water into hydrogen and oxygen—the most important part of plant photosynthesis—consists of several reaction sequences whose primary result is the enrichment of electrons on the outer membrane surface and the enrichment of protons in the internal aqueous volume ("light-induced charge separation")[4]. Part of this reaction is depicted in Figure 2. A chlorophyll molecule on the inner side of the membrane is excited by visible light and in <1 ns donates an electron via a neighboring pheophorbide molecule to a plastoquinone molecule (X320) situated at the outer side of the membrane.

$$\text{chlorophyll}_{\text{inside}} + \text{plastoquinone}_{\text{outside}} \underset{\geq 200\ \mu s}{\overset{<1\ ns}{\rightleftharpoons}} \text{chlorophyll}^{\oplus}_{\text{inside}} + \text{plastoquinone}^{\ominus}_{\text{outside}}$$

This electron transfer is directional—it only proceeds from the inside to the outside. The three reaction centers so far identified (chlorophyll, pheophorbide, X320) are bound to a lipoprotein (molecular weight: 47000), and their positions and mutual alignment are probably largely fixed during photochemical charge separation. This is a prerequisite for vectorial processes. At least two other proteins are responsible for the subsequent electron transport and prevent the slow back reaction (≥ 200 µs). A quinone anion is

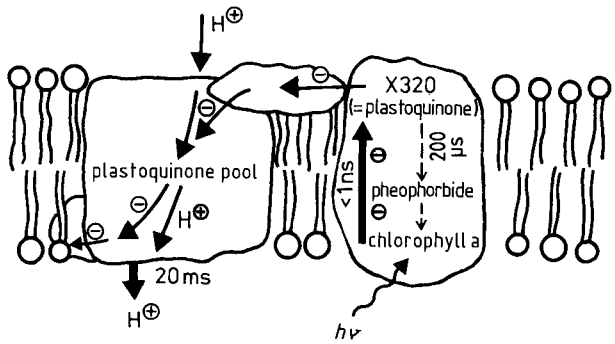
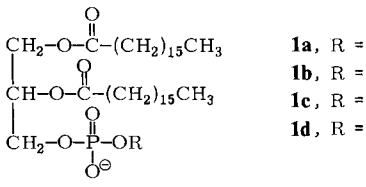


Fig. 2. Part of a model of reaction center II in photosynthesis. Rapid light-induced charge separation is followed by slower proton transport across the membrane. Very little is known about the molecular mechanisms responsible for the vectorial course of the reaction (the forward reactions are much faster than the back reactions).

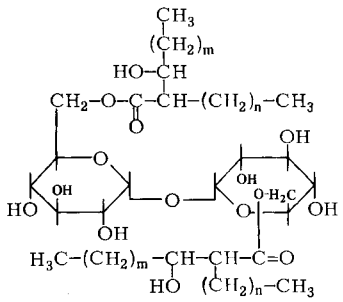
finally protonated by the outer aqueous phase and a proton is transported through the membrane via a plastoquinone pool into the inner aqueous volume. The selective adsorption of dissolved molecules at reactive centers and their action as signals for subsequent reactions, the spatial and time-based organization of reaction centers, and the resulting reversible processes are all fascinating phenomena which are made possible by as yet unknown mechanisms involving the interaction of several membrane proteins; only a few, unsatisfactorily analogous phenomena can be found in bioorganic chemistry.

When compared with the rapidly, selectively reacting proteins, the lipid aggregates constitute a chemically inert filling material. They merely act as a layer separating the two aqueous volumes and as a solvent for the hydrophobic protein moieties. Accordingly, protein-free vesicles have up to now only been studied by physically-orientated chemists[1]. The results of these investigations can be summarized in six points:

1. Phospholipids (such as **1a—d**) or similar water-insoluble amphiphilic natural substances such as **2**[5] aggregate in water to form bilayer liquid crystals which rearrange when exposed to ultrasonic waves to give spherical vesicles (Fig. 3). Natural product vesicles are also called liposomes ("fatty bodies").



1a, R = H
1b, R = $CH_2CH_2\overset{\oplus}{N}(CH_3)_3$
1c, R = $CH_2CH_2NH_2$
1d, R = $CH_2\underset{\overset{\oplus}{N}H_3}{CH}-COO^{\ominus}$



2, m + n = 27-31

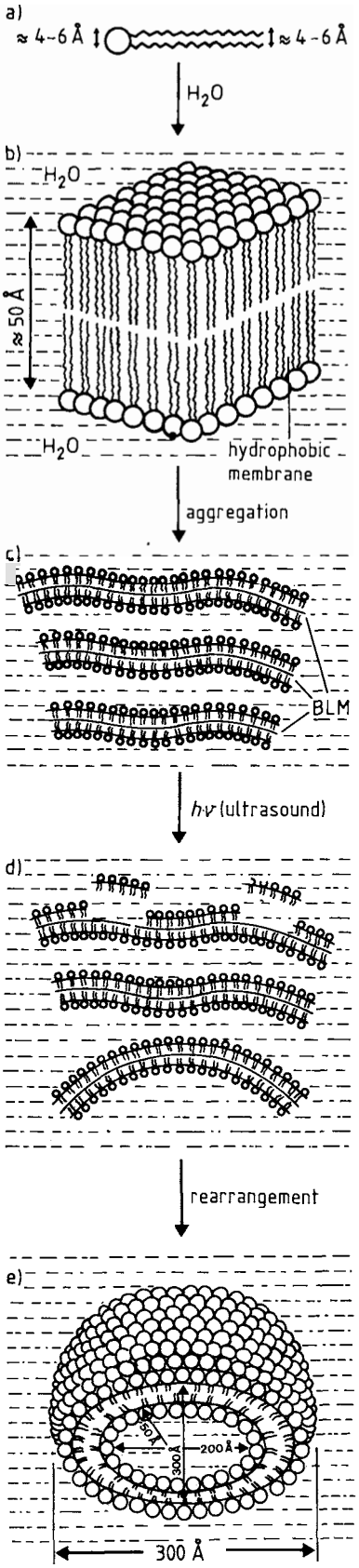


Fig. 3. Vesicle formation by ultrasonic treatment of bilayer membrane (BLM) liquid crystals [24].

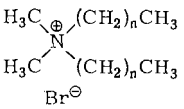
2. The liposome BLMs are extremely thin (thickness ≈ 5 nm).
3. The vesicles are stable for a long time (hours or days) and can be subjected to chromatography and centrifugation.
4. The membrane acts as an efficient barrier for water-soluble compounds but allows water to pass through (osmotic activity).
5. Water-insoluble compounds (e.g. non-polar dyes) can be dissolved in the vesicle membrane.
6. Chemically uniform vesicle membranes display reversible liquid ⇌ liquid-crystalline phase transitions, usually in the temperature range 20–50 °C.

At present it seems that neither the membrane proteins nor the phospholipids will be important topics for future research in organic chemistry. The most important natural phospholipids and their synthetic analogues are known; as far as membrane proteins are concerned, the synthetic problems will be solved by molecular biologists and their structures will be elucidated by spectroscopists. The organic chemist will be limited to helping biophysicists and biochemists (synthesis of pure lipids, systematic cross-linkage of membrane proteins for the structural determination of protein complexes, etc.) or developing artificial vesicle membranes with interesting properties without resorting to the help of nature. This last aspect will be dealt with in the following sections.

2. Reactive Vesicle Membranes

2.1. Head Groups

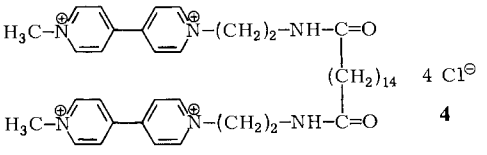
The natural membrane-forming lipids are electroneutral or negatively charged amphiphiles with two fatty acid chains. The breakthrough to other types of membrane-forming compounds was made by *Kunitake* et al. in 1977[6], who demonstrated that tetraalkylammonium salts with two long alkyl residues (e.g. **3**) form vesicles similar to those of the phospholipids. This finding was of importance above all because of its simplicity. It proved that complex interactions between the head groups, which had been studied very intensively in liposomes[7,8], were of little significance in vesicle formation. Furthermore, positively charged vesicles became available for the first time.



3, n = 11, 15, 17

The development of nitrogen-containing head groups continued by trying to localize reaction centers in the periphery of the vesicle membrane to provide a "substitute" for "inner" or "outer" redox-active chromophores such as chlorophyll and plastoquinone. The paraquat derivatives (*N,N'*-dialkyl-4,4'-bipyridinium salts), which have been used extensively in model systems for water reduction[9–11], were introduced as electron acceptors[12,13]. The amphiphile **4** (see Section 3) has two paraquat head groups and is, for example, suitable for vesicle formation. Paraquat can take over the function of plastoquinone, as shown in the biological charge separation depicted in Figure 2. *N,N*-dialkyl-*p*-phenylenediamine head groups (e.g. in the vesi-

cle-forming compound **5**) act as electron donors in analogy with chlorophyll shown in Figure 2[14,15]. Light-destructable vesicles have also been prepared from amphiphiles with diazonioisophthalic acid head groups (e.g. **6**)[14].



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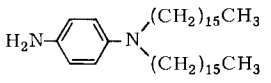

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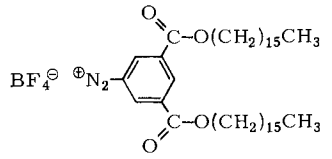
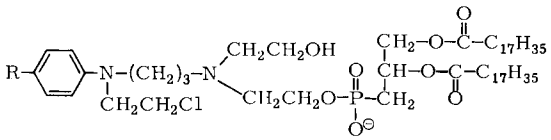


6

The reactive vesicles cited here all display the same special feature; they can only react with water-soluble reagents at the outer membrane surface. Paraquat derivatives can be reduced to viologen radicals with dithionite anions, phenylenediamine derivatives can be oxidatively converted into various dyes with water-soluble couplers, and benzenediazonium derivatives can be degraded by visible light after addition of water-soluble sensitizers (cf. Fig. 4). In all cases an almost quantitative yield of a new head group is obtained at the outer surface of the vesicle membrane, whereas the head groups which are on the inner side remain unchanged. Vesicle membranes exhibiting quantitatively asymmetrical arrangement of the head groups have thus become accessible for the first time. In the case of the semi-reduced paraquat vesicles, electron donors are found only on the outside and electron acceptors are located only on the inside; in the coupling reaction of the phenylenediamine vesicles only the outside is dyed oxidatively, and in the benzenediazonium compound nitrogen is at first eliminated solely by the outer surface.

Vesicles with extremely reactive aziridinium head groups can be synthesized if the aniline derivative **10a** is employed as a deactivated precursor in which the nucleophilicity of the nitrogen atom is markedly decreased by the formyl substituent[18]. Intramolecular substitution of the chlorine atom by the aniline nitrogen does not take place. Vesicles from **10a** are then activated by reduction with $NaBH_4$. The aniline methanol **10b** is produced which reacts with nucleophiles (e.g. proteins containing cysteine) due to the formation of the reactive aziridinium compound.



10a, R = CHO
10b, R = CH_2OH

Nitrogen-containing head groups have also been developed which can reversibly take up protons or metal ions. The ylide **11a** forms yellow (λ_{max} = 399 nm) vesicles which become colorless (**11b**, λ_{max} = 256 nm) on addition of acid. The bipyridinium derivative **12** is red (λ_{max} = 470 nm). As these compounds are water-insoluble, they are also suitable for incorporation into foreign vesicles in which the posi-

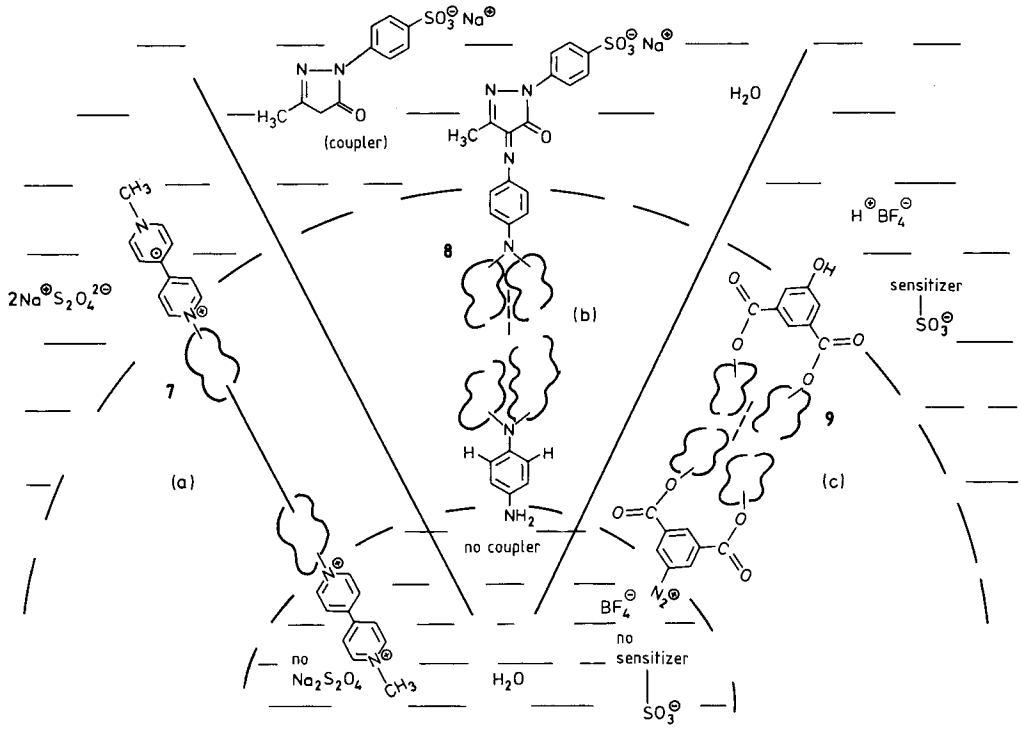
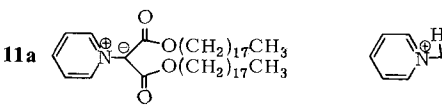
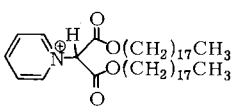


Fig. 4. Examples of reaction products (**7**–**9**) of "exovesicular" head groups of the amphiphiles **4**–**6**. The reactive "endovesicular" head groups are not accessible to membrane-insoluble reagents (examples a, b) or sensitizers (example c).

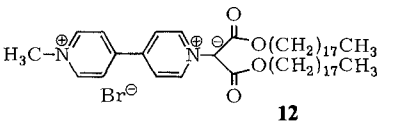
tively charged pyridinium residue lies next to the head groups of the host membrane. The pK_a for protonation of the ylide **11a** is very strongly influenced by the charge of the host groups. In electroneutral vesicles the pK_a value lies close to pH 6, in electropositive vesicles it is pH 4, and in electronegative vesicles it is pH 8[16]. These amphiphilic pH indicators can probably be utilized to detect domains (cf. Section 6).



11a

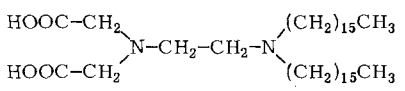


11b

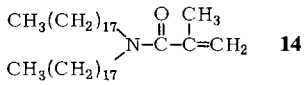


12

The vesicle-forming ethylenediamine diacetic acid derivative **13** complexes metal ions (e.g. $Cu^{2\oplus}$) from the aqueous phase[17]. Since metal ions cannot generally penetrate hydrophobic vesicle membranes, almost any redox-active ions can be fixed on the inner and/or outer membrane surfaces.



13



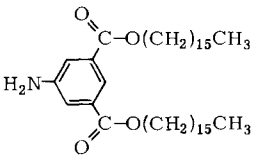
14

Various head groups of vesicle-forming amphiphiles have also been provided with vinyl substituents[19-23]. These terminal groups (e.g. **14**) can be polymerized either solely on the outer vesicle surface with water-soluble radical forming molecules, or on both surfaces with UV light. This does not introduce a new functionality into the vesicles but stabilizes them against the action of detergents and organic solvents (Fig. 5).

2.2. Hydrophobic Centers

Most synthetic vesicle-forming compounds contain two oligomethylene chains ($n > 8$) per head group in analogy with the phospholipids. The diameters of the hydrated head groups in these amphiphiles correspond to those of the hydrophobic chains and are in each case approximately 6 Å. In aqueous media the bilayer membranes thus only exhibit a low degree of curvature; this is regarded as one of the conditions for vesicle formation[24] (cf. Fig. 3). Fatty acid salts with only one oligomethylene chain and ammonium salts with three oligomethylene chains were known to form micelles without internal aqueous volumes and with a high degree of curvature[25-27]. However, there have also been reports of vesicles composed of mixtures of stearic acid and its salts[28] or of trihexadecyl(methyl)ammonium salts[29]. It is not possible to make reliable predictions about the aggregate structures of a new amphiphilic compound in aqueous media on the basis of the data currently available (cf. Section 8).

Whereas appropriate head groups react equally well and rapidly with water-soluble acids, bases, reducing and oxidizing agents and nucleophiles, reactive groups within the hydrophobic membrane are practically inaccessible for water-soluble reagents. This is reflected, for example, in the acid-stability of vesicle membranes in which the head groups and hydrophobic chains are linked by ester bonds. Vesicles from the amphiphiles **15**[14] and **22**[40] are stable for a matter of weeks in aqueous hydrochloric acid at pH 1.5. Basic dyes ($pK_a \approx 5$) are also not protonated even at pH = 1 if they are in vesicular solution[30].



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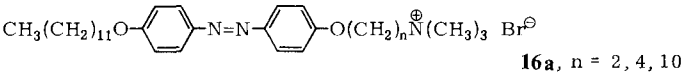
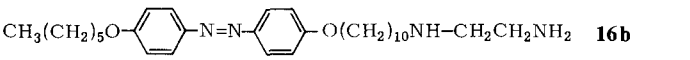
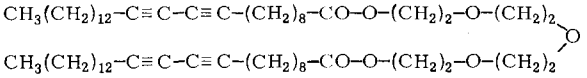


16a, n = 2, 4, 10



16b



17

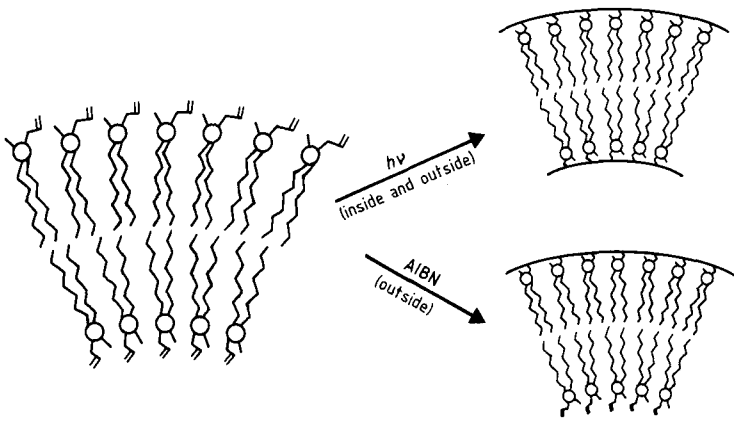


Fig. 5. Polymerization of monomeric amphiphiles at the vesicle surfaces. AIBN = azobisisobutyronitrile (water-soluble radical initiator).

Up to now, light has therefore been used exclusively as a "reagent" for reactions in synthetic hydrophobic membranes. Azomethine[31], azobenzene[45], diene or diyne[20,32-34] chromophores have been employed as reactive centers and were linked to the membrane-forming oligomethylene chains. The *trans*-azobenzene group in vesicles from **16a** underwent 50% isomerization when exposed to ultraviolet radiation to give the *cis* compound, the spherical vesicles simultaneously becoming lamellas. After reverse thermal isomerization, vesicles were reformed, i.e. the enclosed volume of water and the aggregation state of the vesicles undergo reversible changes upon irradiation. In the case of the diyne amphiphile **17** (see Section 8), when liquid crystalline BLMs are subjected to UV radiation (i.e. below the membrane melting point) colored polyene-yne chains are

formed in the middle of both halves of the bilayer. Dye formation does not occur in disordered aggregates.

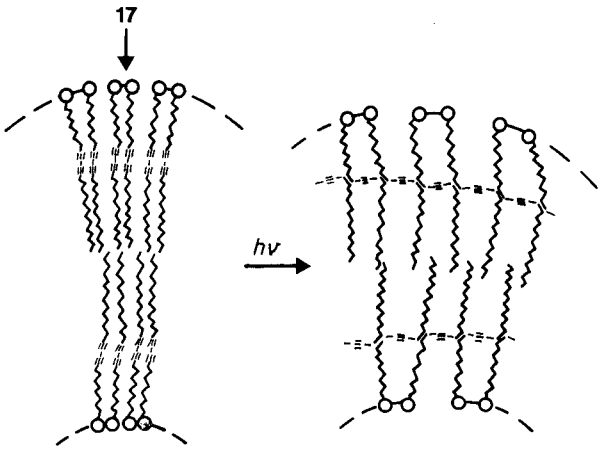


Fig. 6. Polymerization of the monomeric amphiphile **17** to colored polyeneynes in the hydrophobic vesicle membrane.

The membrane interior can be selectively modified in other ways: externally controlled domain formation (cf. Section 6) and regioselective incorporation of foreign molecules (cf. Section 3).

3. Peripheral and Integral Porphyrins in the Nine Regions of Vesicle Solutions

Aqueous vesicle solutions display nine regions or compartments (cf. Fig. 7):

① the outer water volume (bulk volume),
② the aqueous volume in the vicinity of the head groups (hydration sphere, Gouy-Chapman layer),
③ the outer head groups,
④ the hydrophobic membrane close to the outer head groups,
⑤ the interior of the hydrophobic membrane (in bilayer membranes this region can be subdivided into an inner ⑤$_{inner}$ and an outer half ⑤$_{outer}$),
⑥—⑨ the inner regions corresponding to the outer regions ④—①.

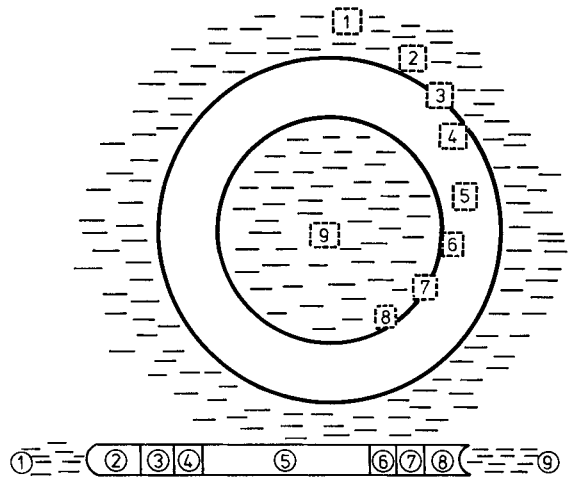


Fig. 7. The nine regions of vesicle solutions.

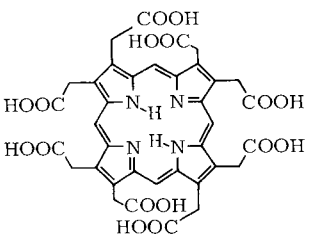
In the case of microvesicles (diameter ≈ 500 Å, amphiphile concentration $\leq 10^{-3}$ M), the volume of the hydrophobic membrane ⑤ and of the enclosed volume of water ⑨ are at least one hundred-fold smaller then the bulk volume ①.

If all or even some of the nine regions defined above could be selectively provided with reaction centers, one of the conditions for synthesizing organized systems without using membrane proteins would be fulfilled. According to Section 2, this has indeed been achieved for the head groups ③ and ⑦ and, in the special case of photochemical reactions, for the hydrophobic compartment ⑤. The other regions can be functionalized by regioselective incorporation of foreign molecules. In vesicles derived from amphiphiles with reactive head groups, the entire surface behaves as a reaction center; the shortest distance to foreign molecules dissolved regioselectively in the membrane is thus fixed, and it is therefore no longer necessary to form domains in order to perform vectorial reactions.

The regioselective incorporation of foreign molecules will now be described using experiments with two water- and membrane-soluble porphyrins as examples; one of these compounds—porphyrin octaacetic acid—is peripherally "attached" to regions ② or ④, the other—mesoviologen porphyrin—is integrally incorporated into the vesicle membrane.

At pH 7, porphyrin octaacetic acid **18**[35] exists in the form of the oligoacetate anion and is water-soluble. The longest wavelength absorbance band (α band) occurs at 616 nm. In the presence of electroneutral or negatively charged vesicles it dissolves in the "bulk" phase ①. When subjected to gel chromatography the porphyrin separates from the vesicle fraction. In solutions of positively charged vesicles the porphyrin oligoanion is bound to the surface of the vesicle membrane region ②. Gel chromatography does not result in separation of the vesicles from the porphyrin. The electronic spectrum of the porphyrin is identical in both cases; the α band is still found at 616 nm.

If aqueous solutions of **18** are acidified (pH 4.5), the porphyrin precipitates out. This precipitation does not occur in the presence of vesicles with surface charge, and the vesicles take up the porphyrin. If the pH is acidified to 5.2, the visible four-band spectrum of the neutral porphyrin chromophore changes to the three-band spectrum of the porphyrin monocation, i.e. one of the two pyrrolenine nitrogen atoms is protonated. Approximately half of the eight acetate substituents should be protonated. The porphyrin monocation is probably still dissolved in either ① or ②. At pH 5 the three-band porphyrin cation spectrum is replaced by the four-band spectrum of the non-protonated porphyrin base. The α band of the visible spectrum is now



18

to be found at 625 nm, which corresponds to the spectrum of porphyrin octaacetate in trichloromethane[36].

It can be concluded from the spectral shift that the porphyrin has migrated from the aqueous medium into the hydrophobic membrane region ④. A protonated nitrogen base is deprotonated on addition of acid. As far as we know, this is the first time that this effect has been observed. The process is completely reversible, i.e. on addition of sodium hydroxide solution the protonated porphyrin cation reappears. If the water-soluble porphyrin octaacetate is enclosed within the inner volume ⑨, acidification results in the same spectroscopic shift 616→625 nm but with some delay because pH equilibration across the membrane requires time (e.g. 15 minutes for lecithin membranes containing cholesterol).

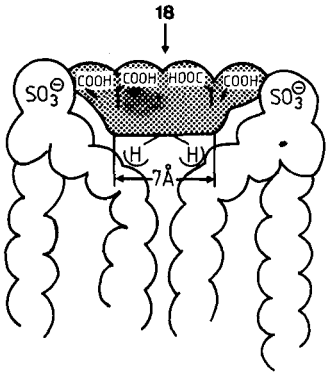
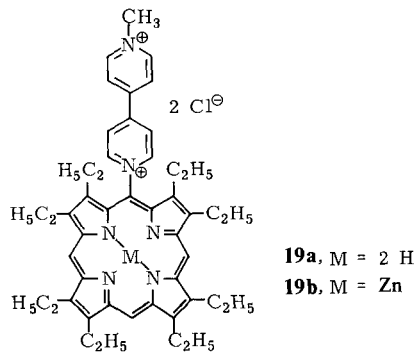


Fig. 8. "Porphyrin octaacetic acid" **18** floats on the hydrophobic surface of the vesicle. The hydrogen atoms directed downwards are from the central NH groups of the porphyrin.

From the reversibility of porphyrin incorporation we deduced that the porphyrin is dissolved peripherally in the membrane (Fig. 8). It is localized in region ④ and not in region ②; this follows from the fact that the porphyrin base is not protonated in strongly acidic media. At pH = 1 the four-band spectrum of the free porphyrin base is still observed. In micellar solutions the pK_a of the porphyrins lies between 4 and 5. Complete formation of the diprotonated porphyrin dication occurs at pH 3 in all cases studied.

"Viologen porphyrin" **19a** is an example of an integral foreign molecule in vesicle membranes[37]. Its zinc complex **19b** is more soluble in water than trichloromethane. In vesicular solutions one would expect **19b** to be localized in regions ① and ②. In fact, the poor reactivity of the porphyrin chromophore towards water-soluble reagents indicates that it is completely taken up by the vesicle membrane. **19a** cannot, for example, be converted into the cation by addition of acid, nor can the metal be removed from the zinc complex **19b**. Since, on the other hand, the substituent in electroneutral or electronegative vesicles can be reduced to a radical by sodium dithionite, it is probably localized on the vesicle surface ③ (cf. Fig. 9). The porphyrin chromophore is accordingly located in regions ④ and ⑤. In analogy with the integral proteins[1,4], it can only be removed from the vesicle membrane if the membrane is destroyed by detergents or solvents.



19a, M = 2 H
19b, M = Zn

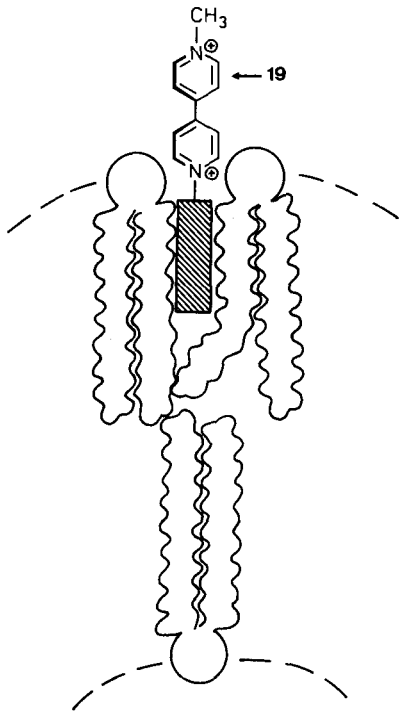


Fig. 9. "Viologen porphyrin" **19** sinks into the hydrophobic membrane of the vesicle.

We have described the special solution behavior of the two porphyrins **18** and **19** in detail to show that vesicular solutions can behave totally differently from micellar solutions or two-phase systems. Dissolved molecules can be localized either entirely within the membrane or in the aqueous medium; distribution between the two phases can be suppressed. This means that another prerequisite for constructing organized systems without proteins has been fulfilled.

4. Monolayer Vesicle Membranes (MLM Vesicles)

If vesicles are prepared using amphiphiles which have hydrophilic head groups at both ends of the hydrophobic chains (trivial name: bolaamphiphiles[38], so called because their shape is similar to that of a South American sling), the resulting membranes consist of a single molecular layer (monolayer lipid membrane, MLM). The MLM vesicles have three advantages compared to the customary BLM vesicles:

1. BLM vesicles grow by fusion and usually precipitate out after a few days. Fusion is hindered in MLM vesicles because the inner hydrophilic head can hardly penetrate the hydrophobic membrane, and it is therefore almost impossible for the amphiphile to migrate from one vesicle to another (cf. Fig. 10). MLM vesicle solutions are stable for a long time under appropriate conditions.

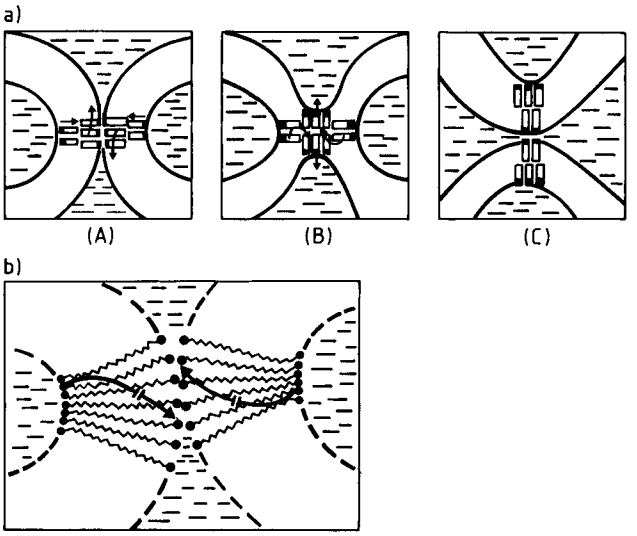
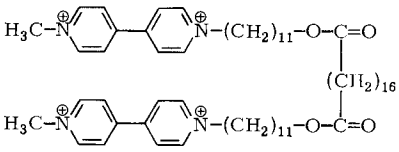


Fig. 10. a) If the vesicle membranes are to fuse, the molecules of the BLM must be able to rotate (or diffuse): (A) aggregate of two vesicles, (B) bridge formation, (C) passage formation (fusion).—b) In monolayer vesicles aggregation is followed by very slow or no diffusion.

2. Monolayer membranes can be considerably thinner than bilayer membranes. The thickness of the thinnest known MLM including the two head groups is 28 Å; the hydrophobic component is less than 20 Å thick. Such thin membranes are of interest because they can be bridged by 15—20 Å long pore-forming compounds. Short "pore-formers" are synthetically more accessible than the 30—40 Å long, pore formers required for BLMs. Many natural products (e.g. porphyrins, carotenes, steroids) have a molecular length of 15—20 Å. Suitable derivatives and their molecular complexes[2,39] can be employed to construct selective systems for conducting electrons, ions, and water-soluble molecules.
3. α,ω-Bisamphiphiles with two different head groups can form totally asymmetrical vesicle membranes: in MLM microvesicles the large head groups (diameter ≤500 Å) form the outer surface, the small head groups the inner surface[40]. In BLM vesicles composed of two different amphiphiles, one type of molecule can only be partially enriched in one half of the bilayer[41].

4.1. MLM Vesicle Formation by "Partial Precipitation"

Aggregates of the symmetrical bolaamphiphile **20a** with two viologen head groups become asymmetrical and exhibit curvature if the counterions are partially exchanged[13]. If, for example, the water-soluble tetrachloride **20a** is titrated with one mol equivalent sodium perchlorate, microvesicles of uniform size are formed spontaneously. The water-insoluble tetraperchlorate **20c** is produced from the monoperchlorate **20b** by adding three mol equivalents perchlorate, and as is to be expected, the curvature of the vesicles disappears. Monolayer crystals can then be observed under the electron microscope (Fig. 11).



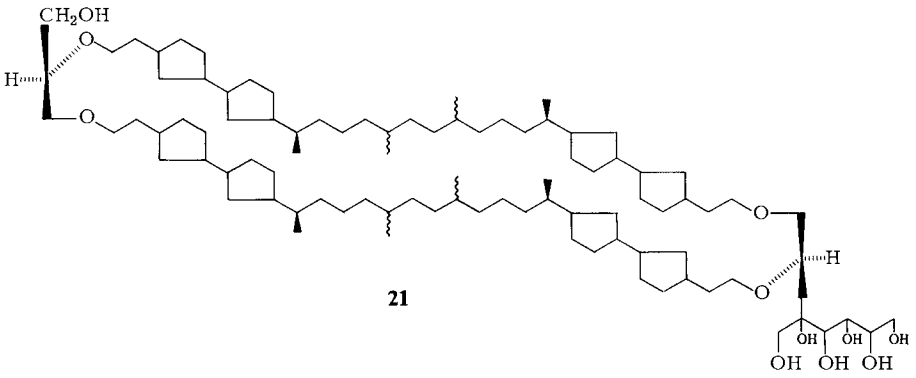
20a: 4 $Cl^{\ominus}$
20b: 3 $Cl^{\ominus}$, $ClO_4^{\ominus}$
20c: 4 $ClO_4^{\ominus}$

f

4.2. Asymmetrical Vesicles-MLMs

The acid- and light-stable membranes of the archaebacterium *Caldariella acidophila* contain the macrocyclic tetraether **21**, which has a (small) glycerol and a (large) nonitol head group. Measurements of asymmetrical current-voltage curves and the specific capacities of black lipid membranes indicate that artificially synthesized membranes are composed of a single molecular layer in which the large heads are localized on one side of the layer and the small heads on the other[43]. This finding seems reasonable in light of the fact that the nonitol terminal with its six hydroxyl groups should crystallize out from *n*-alkane dispersions which are used preferentially for preparing black membranes. Vesicles can be synthesized by means of the partial formation of insoluble salts as described in Section 4.1; similarly, the formation of an asymmetrical membrane begins with the one-sided aggregation of the bolaamphiphile head groups.

The same principle has been adopted for the preparation of an asymmetric membrane consisting of the macro-



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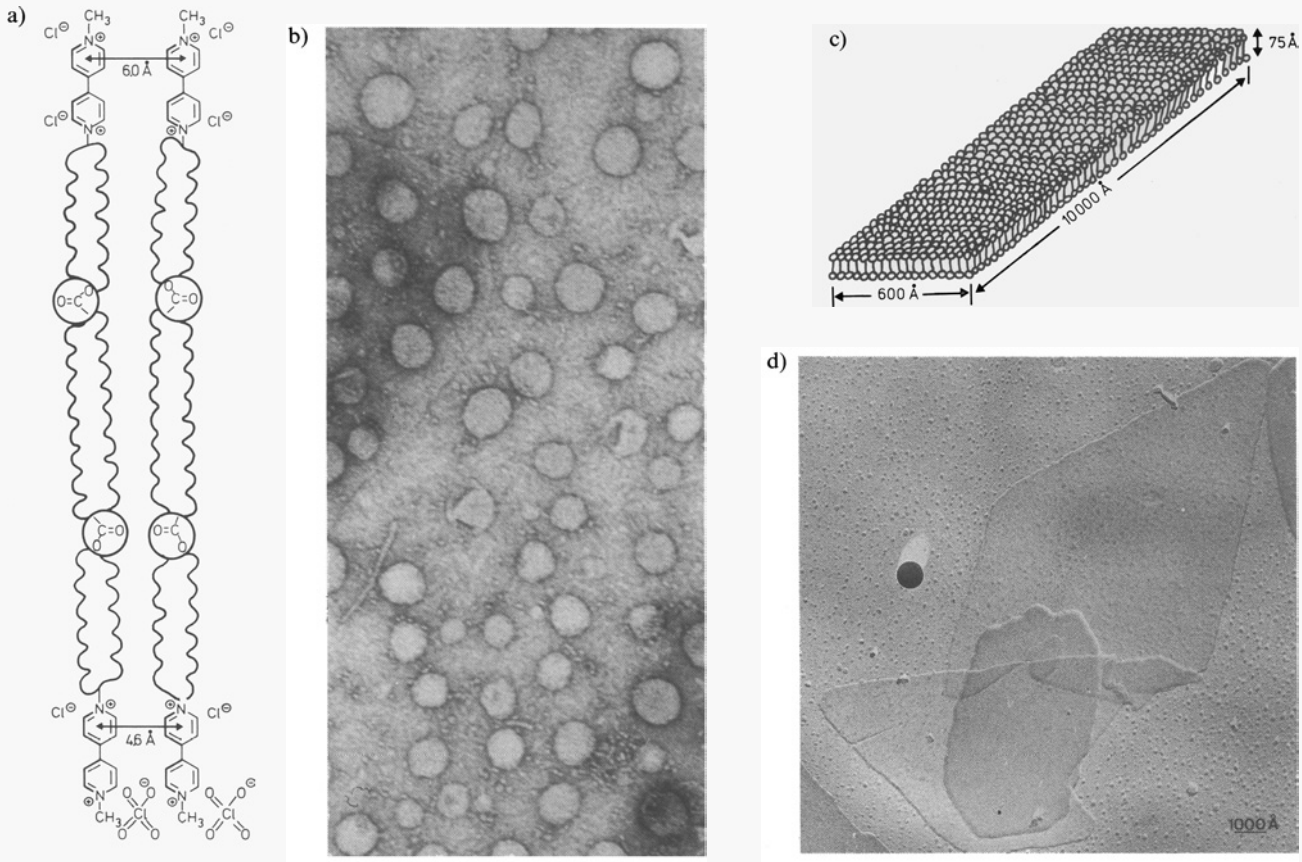
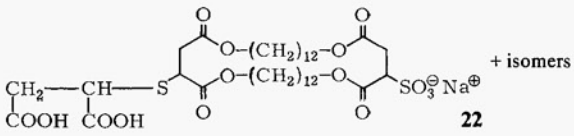


Fig. 11. a) The curvature of monolayer vesicles **20b** is produced by partial formation of insoluble salts (perchlorate inside).—b) Electron micrograph of vesicles from **20b**.—c) The tetraperchlorate **20c** forms monolayer crystals.—d) Electron micrograph of obliquely shadowed monolayer crystals. The white shadow is a measure of the layer thickness. Diameter of latex spheres: 900 Å; thickness of the crystal layer: <100 Å.

tetrolide **22** with a (small) sulfonic acid and a (large) thiosuccinic acid head group[40]. It has been shown that more than 98% of the sulfonic acid head groups lie on the inner side of vesicles derived from this asymmetrical bolaamphiphile (cf. Fig. 12).



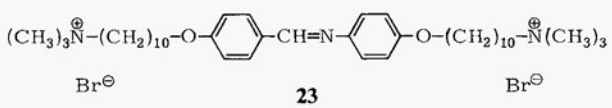
22

This also proves that this membrane is composed of a monolayer[42]. Small-angle scattering measurements with solid **22** gave a thickness of 28 Å for the entire MLM; this corresponds exactly with the all-*anti* conformation of the macrocycle described above. Strangely enough, preliminary ^{1}H-NMR measurements on monolayer vesicles indicate unusually high mobility of the oligomethylene chains at room temperature. This phenomenon is currently being investigated in detail.

4.3. MLM Vesicles with a "Spacer"

Kunitake et al.[31] were only able to obtain the first vesicles from a symmetrical bolaamphiphile, the bisammonium bromide **23**, when cholesterol was added to the emulsion during ultrasonification. The water-insoluble steroid is dissolved in the membrane and is responsible for the "curvature" of the vesicles. A similar effect has been observed in the cheapest of the bolaamphiphiles, the commercially available dimeric acid **24**. After ultrasonic treatment this compound does not form vesicles, and the milky suspension of **24** does not become clear even at very low

Fig. 12. An asymmetrical monolayer vesicle membrane from the bolaamphiphile **22**.



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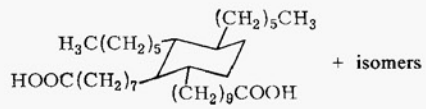


24

concentrations ($\approx 10^{-5}$ M). If, however, a slight excess of the "spacer" cyclohexylamine (cf. Fig. 13) is added, clear vesicle solutions or clear gels are obtained without any difficulty at concentrations of up to 10^{-2} M[44].

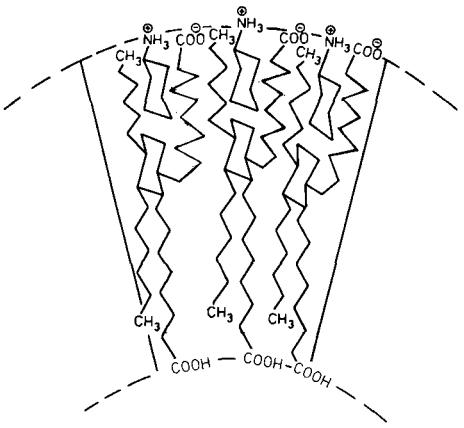
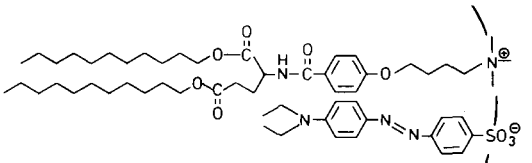


Fig. 13. An example of the "wedge" effect of additives (in this case cyclohexylamine) in the formation of monolayer membranes (in this case from "dimeric acid" **24**).

5. Chiral Superstructures

The vesicle membranes from amphiphiles with chiral head groups are of interest because it is to be expected that chiral superstructures on the membrane surface can react stereoselectively with foreign molecules. The liquid-crystalline vesicle surface would thus have acquired one of the properties of biological receptor proteins. *Kunitake* et al.[45] found indications of a chiral superstructure in vesicles from the glutamic acid amphiphile **25**, which has two oligomethylene chains and an aromatic chromophore in its head group. Circular dichoroism (CD) measurements at room temperature reveal maxima with extremely high specific rotation values ($\Theta_{220} = 360\,000$, $\Theta_{260} = -400\,000$). If the vesicle solution is warmed above the phase transition temperature of 32 °C, a single maximum of much lower intensity appears ($\Theta_{245} = 6000$). Non-vesicular aggregates, which are found below the critical vesicle concentration of 5×10^{-6} M, only show slightly elevated specific rotation values ($\Theta_{260} = -22\,000$). Similar effects have been demonstrated in an alanine derivative **26** with a tetraalkyl ammonium head group and a biphenyl chromophore; this compound forms liquid crystalline platelet-shaped aggregates, not vesicles[46].

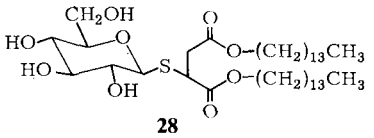
Intensive induced circular dichroism spectra are found when methyl orange is dissolved in chiral vesicles where it is anchored in the membrane by a hydrophobic side chain[47]. The diazo dye head group is probably squeezed into the amino acid surface lattice. Remarkably, an extremely large bathochromic absorbance shift is also observed when methyl orange **27** is incorporated into vesicles from **25**[48]. Below the membrane melting point (20—25 °C) there is a maximum at 488 nm which is displaced to 424 nm at 28—29 °C. This 64 nm shift only occurs when the "hydrophobic spacer" contains a tetramethylene group between the charged head group and the membrane. The methyl orange **27** is probably localized in this ill-defined interspace (region ② or ④?) and fills the gaps left by the narrow "spacer".



25 **27**

Fig. 14. Regioselective incorporation of methyl orange **27** at the chiral surface of vesicles derived from the glutamic acid amphiphile **25**.

Vesicles with carbohydrate head groups are promising chiral receptors because the cyclic rigid conformation and the existence of at least four centers of asymmetry offer particularly high selectivity. Such vesicles have also been prepared from **28**[49] and **29**[50], but as far as we are aware nothing is known about their interactions with water-soluble compounds.



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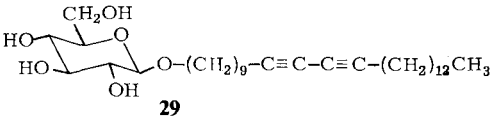

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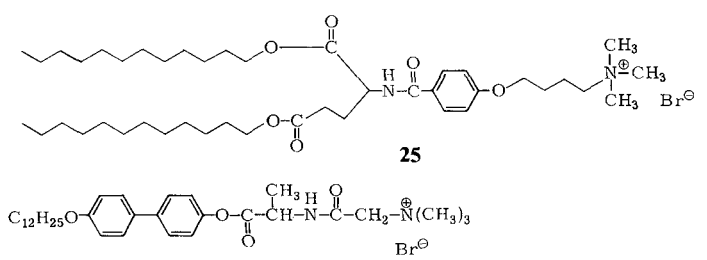
6. Domain Formation

If proteins are not employed to synthesize functional vesicle membranes, other membrane building blocks have to be developed which combine with one another within an inert membrane to produce reactive domains. Only when this has been achieved will it be possible to couple two or more reactions in a vectorial reaction chain in synthetic membranes. Mention should be made of the studies of *Kunitake* et al., who succeeded in verifying and deducing the existence of two types of domain formation.

The first method of systematically organizing parts of the membrane interior is the externally controlled displacement of the membrane building blocks. In mixed BLM vesicles from (inert) dihexadecyl(dimethyl)ammonium bromide and the (reactive) azobenzene amphiphile **16b**, the latter compound exists as a protonated monomer at pH 4 ($\lambda_{max} = 355$ nm). At pH 7, **16b** aggregates in vesicles derived from **3**, and the absorbance maximum shifts to 312 nm, i.e. domains are formed. If copper sulfate is ad-



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ded to the solution at pH 4 the maximum is also found at 312 nm[51]. Sodium sulfate has an analogous effect, but copper chloride is ineffective. This formation and dissolution of amphiphile aggregates in a membrane which is controlled by external protons or divalent anions is the first example of (reversible) domain formation in which the head groups act as receptors (cf. Fig. 15).

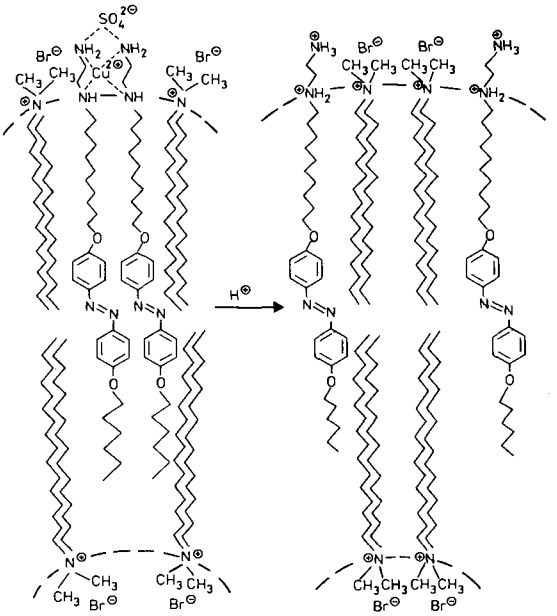
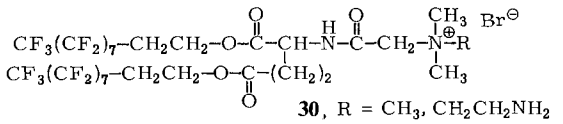
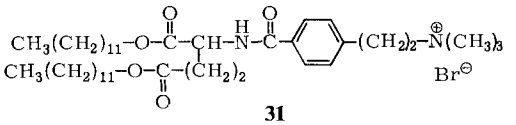


Fig. 15. Domain formation due to the interaction of divalent ions with ethylenediamine head groups. Addition of strong acids destroys the domains.

Vesicle membranes from mixtures of amphiphiles with oligomethylene and oligoperfluoromethylene chains also offer interesting possibilities. It has been demonstrated that fluorinated (**30**) and hydrocarbon (**31**) vesicles do not fuse with one another[52]. This is due to the known "lipophobicity" of fluorinated hydrocarbons[53]. It should be possible to introduce perfluorinated domains into hydrocarbon membranes; the hydrocarbon chains would then bring about (irreversible) aggregation.



30, R = CH_3, $CH_2CH_2NH_2$



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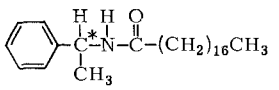
Finally, mention should be made of a report by *Arnett* et al.[54] in which he detected the formation of domains of pure enantiomers in a racemic monomolecular surface layer of **32** by surface pressure measurements. Similar phenomena probably occur in vesicles with chiral head groups (cf. Section 5), but as yet no methods are available for proving that this is the case.



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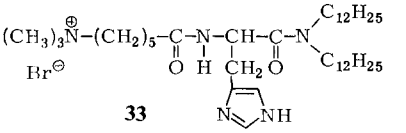
7. Vesicle-Specific Reactions

Reactions will now be described which depend on the ordered structure of vesicle membranes. The cholesterol ester of 4-imidazolecarboxylic acid catalyzes the hydrolysis of *p*-nitrophenyl palmitate if the catalyst and substrate are both introduced simultaneously into tetraalkylammonium vesicles. If vesicles containing the catalyst are mixed with vesicles containing the dissolved substrate, catalysis does not take place[55]. Such differences between the rates of inter- and intravesicular reactions are generally found if the reaction partners can only diffuse slowly out of the vesicle membrane.

p-Nitrophenyl acetate is hydrolyzed by vesicles with SH-containing head groups at pH 7.6 and is bound approximately 1600-fold more tightly than by the comparable micelles[56]. The "hardness" of the vesicle membrane as a reaction matrix as compared with the "soft micelles" is also substantiated by the enantiomer-selective hydrolysis of membrane-dissolved phenylalanine esters by the chiral histidine head groups of **33**. The enantiomer selectivity $k_{obs}(L)/k_{obs}(D)$ in vesicles is 4.4, and in micelles 2.7[57]. If the substrate to be hydrolyzed is fixed in the membrane by means of oligomethylene chains, the enantiomer selectivity can reach values of up to 5.7[58].



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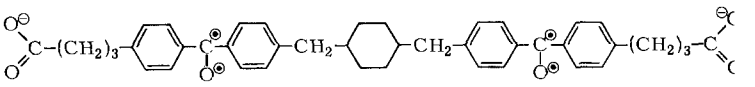
Contrary conclusions about the "hardness" of the vesicle membrane can be drawn from the results of the photochemical incorporation of the benzophenone derivative **34** into oligomethylene chains in vesicles. The excited triplet state of the benzophenone attacks the carbon atoms C6-C12 of a didodecyl phosphate vesicle at random, i.e. **34** takes up the same statistically distributed positions as are found in micelles. The anticipated regioselectivity has only been achieved in planar bilayers[59]. At present there is no plausible explanation for the disordered distribution of **34** in vesicles.



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8. The Structure of Membrane-Forming Molecules

Both thermodynamic and kinetic models for the formation of vesicle membranes[1,25,60] together with comparison of the structures of molecules and their aggregates in aqueous media[61] assume that only amphiphiles form spherical membranes. We do not want to discuss these preliminary "relationships", which do not lend themselves to generalization, and would rather show that this first limitation ("only amphiphiles form vesicle membranes") is not justified.

For many years, *Chang* has been studying "artificial cells" with membranes composed of various water-insoluble polymers[62-64]. They are prepared by shaking a solution of a water-insoluble polymer (nylon, polystyrene, cellulose nitrate) in organic solvents with a relatively concentrated aqueous hemoglobin solution. Well-defined, spherical membranes having a thickness of 200 Å and diameters of up to 0.1 mm are then found in the aqueous phase. Hemoglobin is enclosed within the interior of these cell-like structures. When the organic solvent is removed the spherical aggregates are stable for a long time. Small polar molecules such as urea, but not proteins, can permeate artificial cells made of nylon. "Artificial cells" make highly suitable dialysis membranes on account of their large membrane surface area.

The mechanism responsible for the formation of "artificial cells" has not, as far as we know, been discussed in the literature. We presume that the hydrophobic regions of the hemoglobin take up the polymers and thus transfer them to the aqueous phase. Here the "hydrophobized" polymer complexes aggregate to form sealed membranes. Once these have been formed they become spherical due to the internal colloid-osmotic pressure exerted by the enclosed hemoglobin: the aggregate surface area increases and the membrane becomes thinner. The internal hemoglobin remains enclosed, the hemoglobin in the outer aqueous phase takes up more polymer, and the process is repeated (cf. Fig. 16).

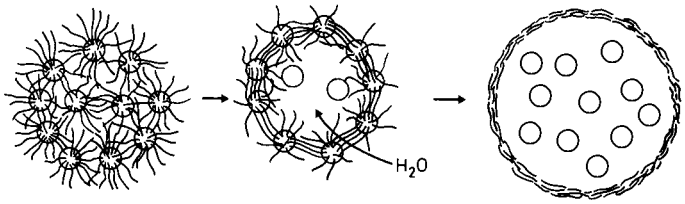
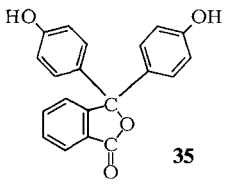


Fig. 16. Hypothetical mechanism for the formation of artificial cells from water-soluble (O) and water-insoluble (∿) polymers.

The "microspheres" described by *Fox* are formed analogously; they consist of "proteinoids", and their appearance under the microscope is similar to that of the "artificial cells"[65]. A "protenoid" is a statistically assembled polyamide which is produced by heating α-amino acid mixtures at 100°C in aqueous phosphoric acid. If the mixture is then cooled slowly, the protenoids do not precipitate out but spontaneously form microspheres with a diameter of approximately 0.1 mm. These protenoid aggregates are also osmotically active and are regarded as the simplest model of the "primitive cell"[66]. They may be formed by the aggregation of hydrophobic proteinoids with each other and with hydrophilic components containing ions; the hydrophobic components could float on the surface of the aggregate, in analogy with the mechanism in Figure 16, to form a sealed hydrophobic skin. This skin could then expand to a membrane as a result of penetration of water into the internal electrolyte solution.

Some observations show[67] that low molecular weight non-amphiphiles which are sparingly soluble in water dissolve when treated with ultrasound and appear as spherical membranes under the electron microscope. Phenolphthalein **35** and carminic acid **36** are examples of such compounds (see also **17**).



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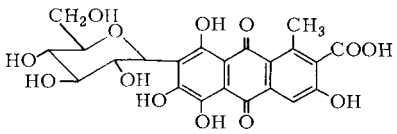

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The objection can be made that "artificial cells" derived from non-amphiphiles are of minor interest because their membranes are probably in a state of disorder. There should not be any striking differences between the membrane surface and the interior. These membranes are probably unsuitable for the organization of several reaction centers. It is, nevertheless, still important to know that the formation of spherical membranes under phase-transfer conditions or after ultrasonic treatment of aqueous suspensions is an inherent property of many water-insoluble compounds.

9. Summary and Outlook

Some intermediate steps have been made towards the ultimate goal that we have defined as "the synthesis of functional vesicles without proteins":

- electron acceptors and donors (head groups, metal ions) can be fixed at defined distances from redox-active dyes in the membrane (metalloporphyrins)
- light can produce structural changes in the hydrophobic membrane (*trans→cis* isomerization of azobenzene units)
- asymmetrical vesicle membranes are accessible ("monolayer lipid membranes" MLM)
- vesicles with chiral head groups can differentiate between enantiomers which distribute themselves between the aqueous phase and the membrane (stereoselective hydrolysis)
- domains can be produced without involving proteins (complexing head groups)
- "dimeric acid" **24** is a cheap amphiphile which can be used for synthesizing large quantities of vesicles (approximately DM 5.00 per kg).

Using these results as a starting point, it seems that the chances of achieving various targets are promising. Individual, complex, functional vesicle membranes have already been described: in *Shilov*'s system for reducing water with the aid of visible light[9-11] the colloidal platinum, the "sacrificial" reducing agent, the dye, and the paraquat have been localized in different vesicle regions (cf. Section 3) and water cleavage has been studied[68,69]. The efficiency and stability of this system are, however, still unsatisfactory. Modified lecithin vesicles have been tested with a view to studying the organ-selective transport of pharmaceuti-

cals in the bloodstream[70]. We are, however, not aware that they have been used in commercially available preparations. Both problems—the light-induced cleavage of water and the transport of pharmaceuticals—are currently under detailed investigation. It is to be hoped that the new synthetic systems will provide practical solutions.

Some new aspects which have arisen from the results of the previously discussed studies seem even more interesting:

- It should be possible to introduce negatively charged polyelectrolyte cores into positively charged vesicles. Vesicles with a nucleic acid core could be of use, e.g., for transporting genetic material through cell membranes.
- Simple pore-forming compounds[2] can be conceived for vesicles with thin membranes (< 20 Å); these substances aggregate to give an ion-permeable pore which can be controlled either by the pH or by signal molecules. Suitable pores in the membrane should provide water-soluble reagents with access not only to the internal aqueous volume of the vesicle but also to the hydrophobic membrane region surrounding the pore. Bases which can be protonated could then, for example, be reversibly expelled from the membrane. The vesicles would act as extremely small, sealable receptacles.
- Using the novel, water-insoluble amphiphiles it should be possible to coat hydrophobic surfaces (e.g. those of plastics) with polar, monomolecular layers.

Realization of these examples will take several years. In most cases not enough is known about the properties of the new amphiphiles and their aggregates to be able to construct complex systems. It is, however, now already evident that the synthetic membranes prepared by *Kunitake* have opened up an interdisciplinary field with interesting prospects.

Our own studies have been supported by the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie, the Kommission für die Förderung der Forschung und des wissenschaftlichen Nachwuchses of the Freie Universität Berlin, and Henkel KGaA, to whom we are extremely grateful. The following competent and imaginative young chemists are thanked for their individual contributions: Dr. H. Bartsch, Dr. E. Baumgartner, H. H. David, K. Ellermann, D. Fritsch, W. Grabow, D. Hosseinpour, W. Kaufmann, V. Koesling, W. Krüger, F. Kühl, T. Lehmann, A. Link, Dr. U. Meding-Angrick, G. Penzlin, G. Pöschl, J. Rosenberg, G. Schönberger, U. Wanja, and W. Weimann, who in examination projects, Diplomarbeiten and dissertations opened up new scientific territory.

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Photochemical Hole Burning: A Spectroscopic Study of Relaxation Processes in Polymers and Glasses

By Josef Friedrich and Dietrich Haarer*

Photochemical hole burning is a special type of saturation spectroscopy in the optical domain having many analogies with NMR methods. The holes, which are burnt with laser irradiation, appear as small indentations in the absorption spectra of dye molecules which are doped into a polymer or glass in minute concentrations. Based on their narrow line width, photochemical holes can be regarded as highly sensitive spectroscopic probes. They can be used to detect small perturbations of the system by external parameters, giving rise to line-shifts and broadenings. Besides the many well documented, spectroscopic applications of hole burning, it may offer interesting future developments for the spectroscopy of biomolecules and for high-density data storage.

1. Introduction

The optical properties of many crystalline and polymeric organic solids are frequently dominated by guest molecules. Guest molecules can either be impurities or doping materials. It has, for example, been known from the early days of low temperature spectroscopy of crystalline organic materials that impurities in low concentrations (10^{-4} mol/mol) can dominate the emission spectra of crystalline host matrices[1,2].

This article deals with hole burning spectroscopy of organic host-guest systems. This spectroscopic method was discovered in 1974 by two Soviet research groups[3-5]. Photochemical hole burning (PHB) spectroscopy is a special kind of saturation spectroscopy: With narrow-band excitation very narrow and stable photochemical holes can be "burned" into the absorption bands of guest molecules. From the line width and line shape of these holes one can obtain information about both the host and guest systems (examples of photochemical holes are shown in Figs. 14, 19, 30, and 31). Most attractive is the very high optical resolution of the hole burning method. In this article we shall mainly focus on the spectroscopy of glasses and polymers, since the high resolution aspects of the new method are especially useful in this field.

In this context we mention that organic host-guest systems are also interesting from the viewpoint of applications. Examples are sunlight-collectors which use organic molecules in polymer or glass matrices to scatter diffuse sunlight into a small solid angle[6,7]. Other, more complex host-guest systems, which are still not completely understood, are polymeric photoconductors[8,9], photographic layers[10], and biological light-harvesting pigments[11].

2. Energy Bands, Localized Excitations, and Phonons

The optical properties of organic solids which are doped with dye molecules are determined both by the absorption

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spectrum of the guest and that of the host. The host states are characterized by bands of bandwith B (Fig. 1). The origin of the band states is the close packing of the host molecules leading to a strong molecular interaction. Band states have dispersive character, i.e. the excitation energy is, in most cases, delocalized over many molecules[12,13] (excitonic state). In contrast to the band states, the excited states of the guest molecules are localized. The localized states are referred to as matrix-isolated because they are more or less decoupled from the host states. Many systems which absorb in the visible region are matrix-isolated. The host system is frequently chosen such that its intrinsic absorption is in the UV region of the spectrum. In the following we will focus our attention on matrix-isolated systems and thus do not have to deal with the band-states shown in Figure 1. We will, instead, focus on the states S_1, S_2 which arise from doping and which are termed extrinsic and will investigate their electronic, vibronic (ν), and phonon satellites. Examples of such systems are amorphous polystyrene (matrix) doped with phthalocyanine (guest) or crystalline durene (1,2,4,5-tetramethylbenzene) (matrix) doped with naphthacene (guest). The concentrations of the dopant are usually very low (10^{-4} to 10^{-6} mol/mol).

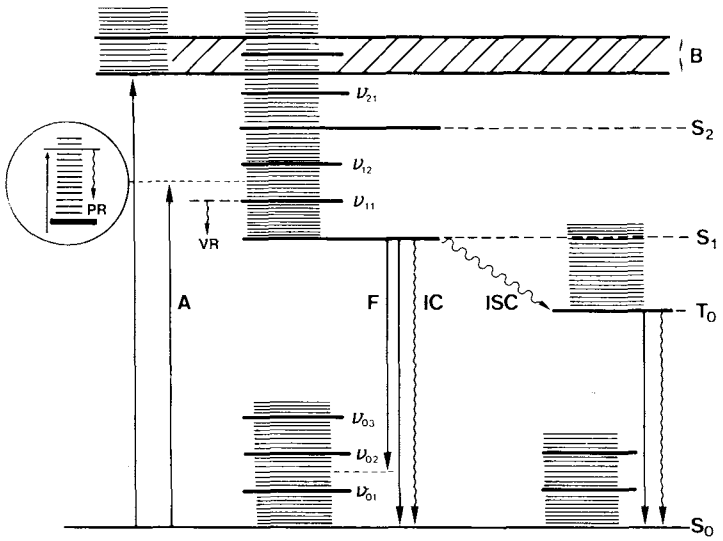
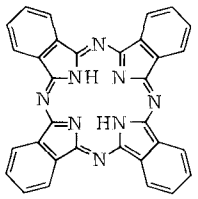


Fig. 1. Energy level scheme of a dye molecule in an organic glass or polymer matrix. B: Electronic band states of the host system (exciton band); S_i, T_i: Singlet and triplet levels of the guest molecule; υ_{ij}: Vibrational levels of the guest molecule in its electronic state i. The levels which appear as a quasi-continuum correspond to phonon states of the host. PR: phonon relaxation; VR: vibrational relaxation; IC: internal conversion; ISC: intersystem crossing; A: absorption; F: fluorescence.

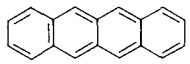
The probability per unit time of an optical transition from the ground state S_0 to an electronic state of the guest molecule (for instance S_1) can be calculated via Fermi's golden rule:

$$P_{10} = \frac{2\pi}{\hbar} |\langle \Psi_1 | \hat{H}_{rad} | \Psi_0 \rangle|^2 g(E - E_1) \tag{1}$$

where Ψ_0 is the electronic wave function of the ground state S_0, Ψ_1 is the wave function of the first excited state, and $g(E-E_1)$ is the normalized absorption line shape



Phthalocyanine



Naphthacene

function. $\hat{H}_{rad}$ characterizes the interaction of the molecule with the radiation field of the light source:

$$\hat{H}_{rad} = -\hat{\mu} \cdot \vec{E}(t) \tag{2}$$

Equations 1 and 2 show that the transition probability P_{10} is proportional to the square of the transition dipole moment $\vec{\mu}_{10} = \langle \Psi_1 | \vec{\mu} | \Psi_0 \rangle$, where $\vec{\mu}_{10}$ is related to the oscillator strength f_{10} of the transition under consideration (see e.g. [14]):

$$|\mu_{10}|^2 = f_{10} [3\hbar e^2/(4\pi m c \bar{\nu}_{10})] \tag{3}$$

where $\bar{\nu}_{10}$ is the optical transition energy in cm^{-1}.

The oscillator strength f_{n0} can be obtained directly from measurements of the extinction coefficient ε_{n0}. The index n labels the transition $n \leftarrow 0$ whose absorption spectrum is being considered. One can write

$$f_{n0} = \ln 10 \cdot \frac{4\varepsilon_0 m c^2}{e^2 N_A \cdot n_0} \int_{-\infty}^{\infty} \varepsilon_{n0} \, d\bar{\nu}_{n0} \tag{4}$$

where N_A is Avogadro's number, n_0 is the refractive index of the material, and ε_0 is the dielectric constant.

So far, only electronic excitations have been considered (with the additional assumption of dealing with allowed transitions). Besides the electronic excitations, molecular spectra also reflect vibrational degrees of freedom. The relative intensity of the electron-vibration bands is given by the Franck-Condon principle, which determines the coupling of the intramolecular vibrations of the guest molecules, which have well-defined energies up to several thousand wave numbers; the same principle also determines the coupling of lattice modes *(phonons)* to the electronic transition. Typical phonon energies lie in the range 10 to 100 cm^{-1}; they have a continuum character (Fig. 1). In the following we consider the coupling of a "normal lattice mode" q_i of frequency Ω_i. Figure 2 shows two electronic energy levels E_0 and E_1. On each of these levels one can build up excitations of harmonic oscillators with energies $\hbar\Omega_i$. As can be seen from the figure, an electronic excitation from E_0 to E_1 leads to a change in equilibrium distance from $q_i = 0$ in the ground state to $q_i = q_{i0}$ in the excited state. The corresponding energy change is proportional to the force constant $K_i = m_i \Omega_i^2$ of the harmonic oscillator with frequency Ω_i and mass m_i:

$$E_{pi} = \tfrac{1}{2} K_i q_{i0}^2 = \tfrac{1}{2} m_i \Omega_i^2 q_{i0}^2 \tag{5}$$

The energy E_{pi} corresponds to half the Stokes-shift between the maxima of the absorption and emission spectra.

If one wants to calculate optical spectra, the transition probabilities to the vibrational levels $\Phi_{ni}(\nu)$ have to be cal-

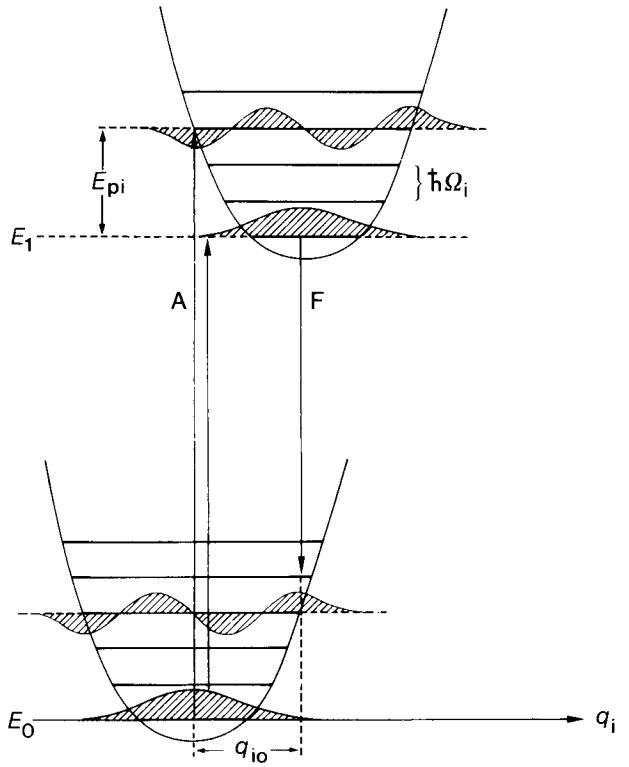


Fig. 2. Energy diagram for interpreting the phonon sideband spectra in terms of configurational coordinates: q_i represents a normal mode of the lattice. The arrows correspond to zero-phonon and three-phonon transitions in absorption and emission, respectively (see text).

culated. Here, the index n stands for the electronic excitation, index i labels the i-th lattice mode of frequency $\hbar\Omega_i$, and v labels the number of excited vibrational quanta in the mode i.

To simplify the calculation, several approximations have to be introduced. The first, is the *harmonic approximation,* which assumes that all lattice modes are independent of another and are described by parabolic potentials; the second, is the *low temperature approximation,* which assumes that in the lowest electronic state only the zero point vibration is excited; the third approximation is the assumption of *linear electron-phonon coupling,* which assumes identical force constants in the ground state E_0 and excited state E_1.

In most experiments the above assumptions are well fulfilled. (Some details have to be modified for calculation of the optical line widths.)

The transition probability $\Psi_1 \leftarrow \Psi_0$ can be calculated using the Franck-Condon principle, which states that the electronic excitation is so rapid that the lattice coordinates q_i cannot follow. Hence, in Figure 2 the optical transitions can be symbolized by vertical arrows. With the above assumptions the transition probability can be calculated from the lowest vibrational state (00) to the vth level of the lattice mode q_i in the excited electronic state

$$P_{1i,00}(v) = \frac{2\pi}{\hbar} |\langle \Psi_1 \Phi_{1i}(v)|\hat{H}_{rad}|\Psi_0 \Phi_{0i}(0)\rangle|^2 g(E - E_1 - v\hbar\Omega_i)$$

$$= \frac{2\pi}{\hbar} |\langle \Phi_{1i}(v)|\Phi_{0i}(0)\rangle|^2 |\langle \Psi_1|\hat{H}_{rad}|\Psi_0\rangle|^2 g(E - E_1 - v\hbar\Omega_i) \quad (6)$$

The line shape function of equation (6) leads to narrow peaks with spacing $\hbar\Omega_i$, characterizing the absorption spectrum of the electronic transition $1 \leftarrow 0$. The intensity of the narrow peaks is given by the overlap of the harmonic oscillator wave functions of Figure 2. Figure 3a shows the transition probability for two modes i and j calculated with the aid of equation (6). For the sake of clarity, we have drawn the absorption and emission spectra separately. In order to obtain the complete spectrum, all modes i have to be summed. Figure 3b shows a spectrum which results from superposition of modes i and j. The *zero-phonon line* ($v=0$) dominates the whole spectrum. There are two reasons for this: First, the zero-phonon lines of all lattice modes i,j... add at the electronic origin $E_1 - E_0$. Second, the width of the zero-phonon line is narrower because its relaxation is prohibited to some extent by the large energy splitting $E_1 - E_0$. The adjacent lattice states spaced by $n\hbar\Omega_i$ and $n\hbar\Omega_j$ relax on a much faster time scale. The envelope of all phonon excitations is termed a *phonon sideband.*

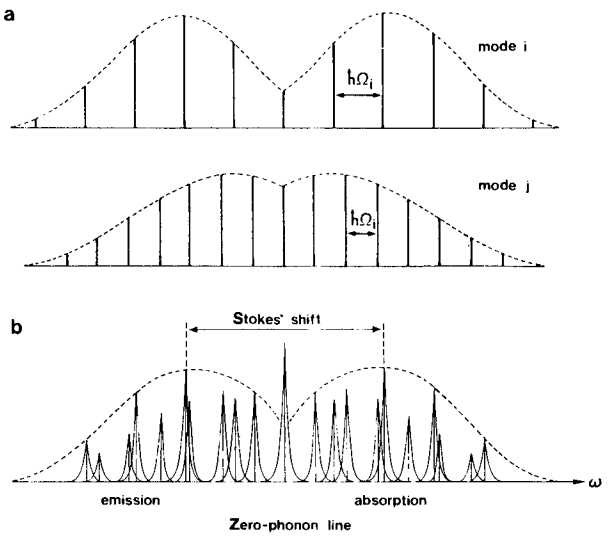


Fig. 3. a) Transition probabilities for two lattice modes i and j [see eq. (6)]; b) superposition of the two modes i and j. The intensities of both modes add up at the zero-phonon frequency (line coincidence); however, they do not add up in the multi-phonon transitions.

We are interested in calculating the line shapes quantitatively. Figure 4 therefore shows a typical line profile of an electronic transition including its phonon sideband (see Section 3). An important quantity is the Lorentzian zero-phonon line $z(\omega)$ with its integrated area α and its line width γ. A second characteristic feature is the phonon sideband $p(\omega)$ with its integrated area $(1-\alpha)$. The line shape of the phonon sideband is given by the overlap integrals of equation (6); these correspond to a Poisson distribution (see e.g. [15]). In many cases an approximation using a Gaussian profile is completely adequate[15, 16, 17]. The total line shape of the $1 \leftarrow 0$ transition is a normalized superposition of $z(\omega)$ and $p(\omega)$. The transition is characterized by the Debye-Waller factor α, which gives the relative intensity I_0 of the zero-phonon line normalized by comparison with the total intensity I_g. Figure 5 shows an experimentally determined guest-host phosphorescence spectrum[18]: In Fig-

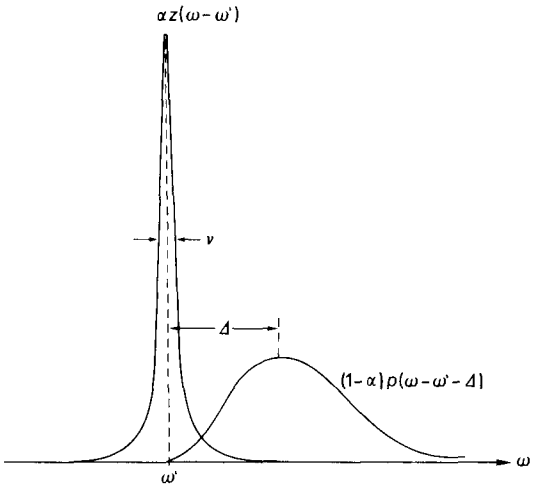


Fig. 4. General line shape function of an electronic excitation of a guest molecule in a solid host matrix: Schematic view of a zero-phonon line and phonon sideband.

ure 5b the zero-phonon line is the dominating feature and in Figure 5a the phonon sideband dominates. The first case is referred to as *weak* electron-phonon coupling and the second, as *strong* electron-phonon coupling. For high-resolution hole burning spectroscopy one needs systems with strong zero-phonon lines to yield the required optical resolution.

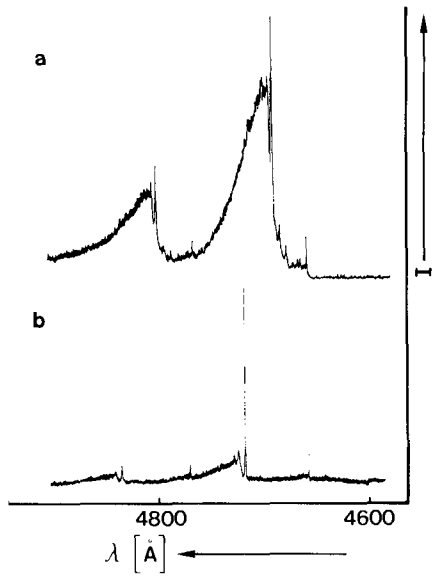


Fig. 5. Phosphorescence spectra of two trap states in the charge-transfer single crystal naphthalene-tetrachlorophthalic anhydride. a) Purified material: The trap state is strongly coupled to the lattice, i.e. the relative intensity of the phonon sideband is large. b) Unpurified material: The trap state is weakly coupled to the lattice; the relative intensity of the phonon sideband is small. A trap-state is a localized excited state of a crystal and can, for example, be produced by doping or by the presence of impurities in natural abundance.

The Debye-Waller factor α is extremely relevant for hole burning experiments. It follows explicitly from equation (6) if one compares the contribution of all modes to the zero-phonon line, namely $\sum_i |\langle \Phi_{1i}(0)|\Phi_{0i}(0)\rangle|^2$, with the total intensity. Since the total intensity is normalized, one obtains

$$\alpha = I_0/I_g = \sum_i |\langle \Phi_{1i}(0)|\Phi_{0i}(0)\rangle|^2 \tag{7}$$

As $T \to 0$, α can readily be calculated (see e.g. [19]), giving

$$\alpha(T=0) = \exp\left(-\frac{1}{2}\sum_i \frac{m_i \Omega_i}{\hbar} q_{i0}^2\right) \equiv \exp(-S) \tag{8}$$

If only a single phonon mode is considered, S has a simple physical interpretation: It corresponds to the number of vibrational quanta which are excited in the maximum of the phonon sideband. If the case shown in Figure 2 is taken, one gets an S-value of 3. The "Franck-Condon gap" Δ_i (half the Stokes-shift) can also be calculated from the one-mode model shown in Figures 2 and 4:

$$\Delta_i = S_i \hbar \Omega_i \tag{9}$$

For S-values >5, one is dealing with strong electron-phonon coupling. In such cases one cannot expect to observe a narrow zero-phonon line [eq. (8)]. Especially in the case of rather strong electron-phonon coupling, the "one-mode" model is quite often good, because usually a single mode couples more strongly than the others and, thus, dominates the optical spectrum.

3. Optical Line Shapes in Perfect Lattices

The optical properties of guest molecules are strongly influenced by the nature of the host lattice. For this reason one can consider a guest molecule as a sensitive probe for the structure and dynamic properties of the host lattice. To exemplify the host-guest interaction we consider a matrix-isolated molecule. Its excited state lifetime T_{10} is given by various relaxation processes, such as fluorescence (F), intersystem crossing (ISC), internal conversion (IC), and vibrational relaxation (VR) (see e.g. [20] and Fig. 1). From Heisenberg's uncertainty relation the *natural line width* γ_0 is

$$\gamma_0 = 1/T_{10} \tag{10}$$

γ_0 is given as the full width at half-height (FWHH) and is expressed in units of $2\pi/s$. For singlet states S_1, lifetimes of 10^{-8} to 10^{-9} s are typically encountered; therefore, the γ_0 values lie in the range 100 MHz to 1 GHz. If one wants to measure natural line widths, typically an optical resolution $\omega_0/\gamma_0 = 10^7$–10^8 is required (ω_0 is the frequency of the optical transition).

So far we have neglected the influence of the lattice, which reduces the lifetime T_{10} to T_1 by introducing new radiationless decay channels[21]. In addition to the relaxation phenomena, the host-guest interaction introduces mechanical strain; it also leads to electrostatic and to van der Waals' interactions, shifting the molecular level by a "solvent shift" D[22]. In the case of a perfect host lattice, all molecules experience identical shifts and, hence, their optical transitions coincide (Fig. 6). The width of this ideal line at $T=0$ is given by its lifetime T_1. Upon increasing the temperature, the thermal motion of the lattice increases and leads to an additional line-broadening mechanism, termed *phase relaxation* (see e.g. [23,24]). We would like to describe

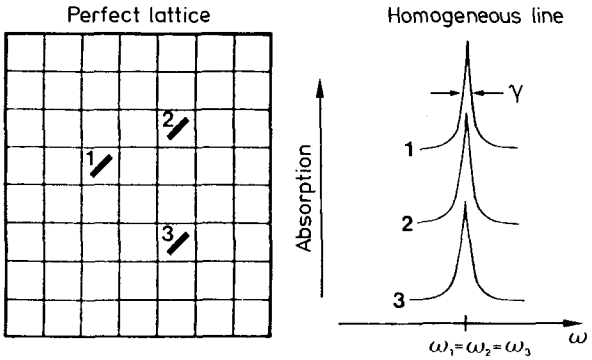


Fig. 6. Schematic view of the optical absorption lines of three (identical) guest molecules in a perfect crystal. The three lines have identical transition frequencies.

this relaxation process on a qualitative level. If a whole ensemble of molecules is excited with a coherent light source, an ensemble of molecules oscillating in phase with each other and with the external light source results. In this way, a macroscopic polarization $\vec{P}$ is induced which can be expressed as a vectorial sum of all molecular transition dipole moments

$$\vec{P}=\vec{P}_0 e^{i[(E_1-E_0)/\hbar]t}; \qquad \vec{P}=\langle\vec{\mu}_{10}(t)\rangle \tag{11}$$

Equation (11) describes a complex vector rotating with the laser frequency

$$\omega_L=(E_1-E_0)/\hbar$$

(In a coordinate system which rotates with frequency $\omega_{01}=(E_1-E_0)/\hbar$, the fast-phase factor of eq. (11) is 1; see Section 6.)

If an individual molecule of the large ensemble is considered, a thermal motion in its neighborhood will change its energies from E_0 to $E_0+\Delta E_0$ and from E_1 to $E_1+\Delta E_1$. As a consequence, the characteristic frequency of the transition moment is shifted by the amount $\varepsilon=(\Delta E_0-\Delta E_1)/\hbar$. This "detuning" leads to a phase loss of the molecule. Since the thermal motions of the lattice have a stochastic nature, ε is also stochastic and thus leads, within the time interval T_2^* *(phase relaxation time),* to a statistical distribution. During this time the various transition moments become out-of-phase and, thus, the macroscopic polarization drops to $\vec{P}_0/e$.

These considerations are only valid if the lattice fluctuations can be regarded as being stochastic, i.e. if a motion at time $t+t'$ is completely independent of one at time t. This is valid for $t'\gg\tau_c$, where τ_c is the correlation time describing lattice fluctuations. If one applies Heisenberg's uncertainty principle to the decay of the macroscopic polarization,

$$\gamma_h=1/T_2\geqslant 1/T_1 \tag{12}$$

results, where γ_h is the *homogeneous line width:* this reflects the dynamic influence of the lattice on the probe molecule. As mentioned previously, $T_2\rightarrow T_1$ as $T\rightarrow 0$ K, which is a consequence of the third law of thermodynamics. At $T=0$ K the stochastic motions of the lattice are "frozen out". The lattice has a "sharp" energy level and thus its entropy is zero.

The lattice fluctuations are caused by phonons, which at thermodynamic equilibrium are created and destroyed with the boundary condition of a mean occupation number $\langle n\rangle$ given by

$$\langle n\rangle=1/(e^{\frac{\hbar\omega}{kT}}+1) \tag{13}$$

One can, therefore, argue that the fluctuations of an excited state are caused by quasi-elastic scattering via phonons[25,26,27]. This is shown schematically in Figure 7: A phonon is absorbed in the ground state Ψ_0 of the scattering center. This changes the energy of the state Ψ_0 by a small amount ΔE_0. If the coupled system of molecule plus phonon absorbs a light quantum, it does so at an energy $(E_1^*-E_0^*)$, which is slightly different from that of a "phonon-less" transition at (E_1-E_0). This is due to a slightly different charge distribution in the probe molecule in the excited state. Since the phonon is re-emitted to the lattice, one refers to the above process as elastic scattering. These scattering processes lead to an increase in line width of the order $(\langle(\Delta E_0-\Delta E_1)^2\rangle)^{1/2}$. Clearly, as $T\rightarrow 0$ K such scattering processes disappear [eq. (13)], since at $T=0$ no thermal phonons are available.

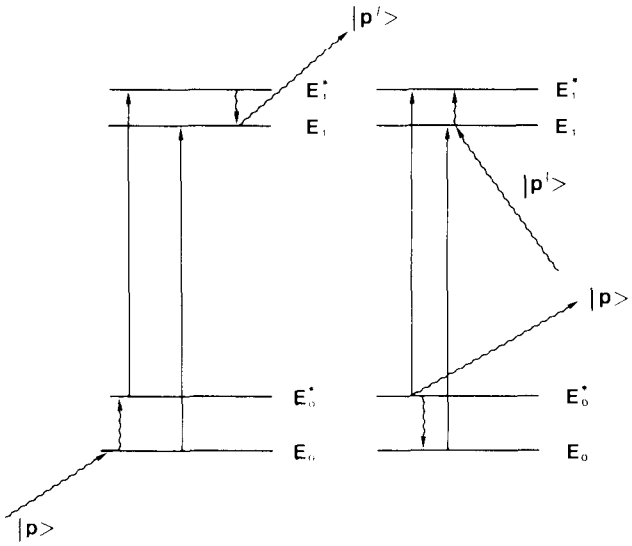


Fig. 7. Energy diagram for elastic phonon scattering involving two different electronic levels (0,1). The electronic transitions are drawn with straight arrows, the phonon transitions with wiggly arrows.

In this case, γ_h is, according to eq. (12), exactly determined by the inverse of the lifetime T_1. The discussion presented here shows that the homogeneous line width as a function of temperature is a characteristic probe for dynamic processes in the lattice.

At this point we want to make some remarks concerning the line widths. We have shown earlier in this section that the phase relaxation is given by the decay of the macroscopic polarization. In mathematical terms, this time dependence is described by the autocorrelation function of the dipole moment[28]:

$$C(t)=\langle\vec{\mu}(0)\vec{\mu}(t)\rangle \tag{14}$$

The autocorrelation function can be viewed as a mathematical scheme which correlates a physical parameter (here the macroscopic dipole moment) at time t with the same quantity at $t=0$. The average brackets in equation (14) reflect that C is a macroscopic quantity. The optical line shape is given by the Fourier transform of the autocorrelation function of the dipole moment:

$$L(E) = \frac{1}{2\pi} \int_{-\infty}^{+\infty} C(t)\, e^{-iEt/\hbar}\, dt \tag{15}$$

The decay of C is given by T_2^* and T_1 for times $t \gg \tau_c$[29]. For exponential decay of C, $L(E)$ is given by a Lorentzian line shape. If only two states are considered (i.e. Ψ_0, Ψ_1), equation (15) yields directly

$$L(E) = |\vec{\mu}_{01}|^2 g(E - E_1) \tag{16}$$

where g is the normalized line shape function introduced in equation (1).

4. Optical Spectra in Glass Matrices

The optical spectra of guest molecules in glassy matrices are very different from those in crystalline matrices. To understand this phenomenon, one has to grasp the basic difference between a crystal and a glass: The glass transition is not a real phase transition, even though many thermodynamic properties exhibit discontinuities there[30-32]. The glass transition has certain kinetic aspects which we will discuss briefly. If the temperature of a host-guest system is lowered through the range in which the glass transition occurs, the intrinsic viscosity of the liquid increases by many orders of magnitude. The liquid finally freezes at a fictitious temperature T_x. To define this temperature, we have to perform a *gedankenexperiment:* We freeze the liquid slowly, maintaining thermodynamic equilibrium. The increasing viscosity of the solution leads to increasing relaxation times and, hence, equilibrium can only be maintained down to a temperature T_x. At this point we quench the liquid to temperatures below which the liquid freezes, i.e. is in a glassy state. We can then assume that the potential distribution of the glass corresponds to that of the liquid at temperature T_x. Clearly, T_x depends on the cooling rate. The thermodynamic properties of a glass therefore depend on the sample's cooling history. Hence, a glass is a *non-equilibrium state*[33]. Each cooling cycle leads to a different point in the configurational space. Figure 8 shows a cross section through the configurational space along a coordinate q. The figure shows that a glass has entropy even at absolute zero[33], since it can occupy various configurations. This is in contrast to the typical situation for a crystal, whose configuration is well defined at $T=0$. In a glass one can think of relaxation processes (e.g. between the states 1 and 2 of Fig. 8) leading to an energy uncertainty, which will eventually be reflected in the optical spectra of glassy materials.

Figure 8 suggests an approach to a quantum mechanical interpretation of the glassy state[34,35]. The random potential given in Figure 8 can be represented as a distribution

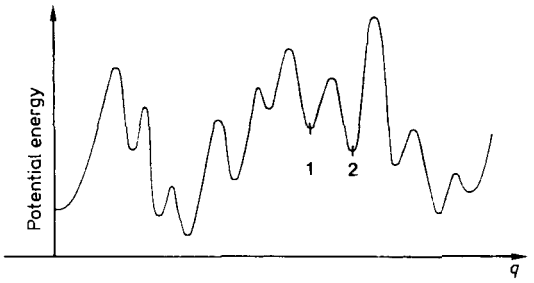


Fig. 8. Cross section through the configurational space of a glass along a fictitious coordinate q (see text).

of double-well potentials. The dynamics of the glassy state can be modeled by the dynamics of double-well potentials whose parameters are determined by an appropriate distribution function. The physics of the systems is determined by this distribution function[36,37]. Measurements of specific heat (C_p) below 1 K allow conclusions to be drawn about the glass distribution function, but only over narrow energy ranges[37,38] (see Section 13).

For double-well potentials the nomenclature of "two-level systems" (TLS) has been used to describe the two lowest eigenstates of the system. The TLS states seem to have a high spectral density at very low energies and this is responsible for the so-called thermal anomalies: At temperatures below 1 K the specific heat increases linearly with temperature (crystal $\sim T^3$) and is time-dependent[39,40] and the thermal conductivity increases with T^2 (crystal $\sim T^3$); both the velocities of sound and that of light in glassy systems are temperature-dependent[41]. In the past few years it has become clear that TLS also influence the optical properties of amorphous materials[42-46].

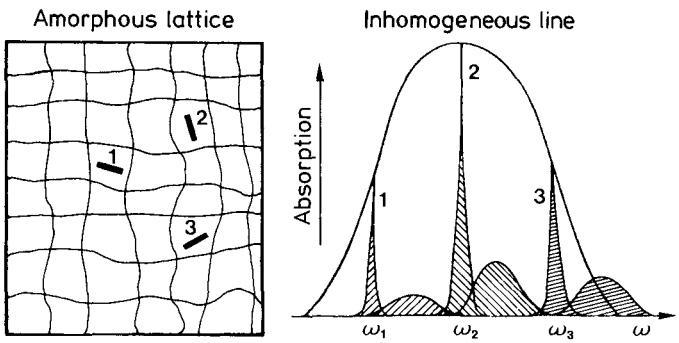


Fig. 9. Schematic view of the optical absorption of three (identical) guest molecules in an amorphous host. In contrast to the situation in a crystalline lattice, the lines appear at different transition frequencies. The broad sidebands represent the phonon spectra of molecules 1, 2 and 3, respectively.

As pointed out previously, the microscopic environment of a "solvent" molecule in a glass is random (Fig. 9). Therefore, the "solvent shift" D is, in contrast to the situation encountered in crystalline systems, not uniform but given by a statistical distribution (site distribution). The latter is usually assumed to be Gaussian:

$$G(D) = 2\sqrt{\frac{\ln 2}{\pi}} \cdot \frac{1}{\Gamma} \exp\left\{-\frac{4(D-D_0)^2 \ln 2}{\Gamma^2}\right\} \tag{17}$$

In organic glasses this distribution can span several hundred wave numbers. Similar distributions are observed for crystals with imperfections; however, in the latter case the line width is only of the order of several wave numbers. The width of the site distribution Γ (full width at half-hight, FWHH) is termed the *inhomogeneous* line width. Figure 9 gives a schematic view of the spatial fluctuations of the site geometry and the corresponding optical absorption profiles. (Besides the spatial fluctuations, there are also fluctuations in the time domain which are responsible for the *homogeneous* line width.) One goal of this article is to discuss methods for measuring individual line shape functions (1, 2, and 3 in Fig. 9) despite the inhomogeneous line broadening phenomena which characterize the glassy state and which, under normal conditions, mask the line shape. A second goal is to relate the line shape profiles to the specific degrees of freedom of the amorphous host matrix (TLS).

5. The Optical Two-Level System Interacting with a Coherent External Field

In the following we briefly compare spectroscopic experiments in the frequency domain (especially optical hole burning) with those in the time domain. Both types of experiments can, under certain conditions, give the same information.

The mathematical framework necessary to describe optical relaxation processes is almost identical with that used in the theory of spin resonance phenomena. This was proved by *Feyman et al.*[47] who described the general equivalence between an optical two-level system and a spin-1/2 system. For the optical two-level system we define the initial and final states as the electronic ground state and the lowest allowed excited state (S_1), respectively. Bearing the basic properties of a spin 1/2 system in mind, we point out some qualitative differences between the optical two-level system and a spin-1/2 system.

a) For optical two-level systems the relation $E_1 - E_0 \gg kT$ holds in general. The longitudinal relaxation time T_1 therefore exists only for the excited state E_1 with a measurable rate. It corresponds to the optical lifetime. The lifetime of the ground state can be assumed to be infinite (i.e. no measurable thermal population of E_1). In other words, the two-level system tends towards a state of complete "polarization" if no radiation is absorbed. A state of complete polarization can, in the case of spin resonance, only be achieved at infinitely high magnetic fields (or infinitely low temperatures). In this highly polarized state all spins are aligned. A completely different picture applies to energy-conserving dephasing processes, which can occur in both the ground *and* excited states. Dephasing processes are usually due to phonon scattering. For optical systems the condition $T_2 = T_1$ is only fulfilled in exceptional cases (i.e. at very low temperatures).
b) In optical systems spontaneous emission processes play an important role. This behavior is quite different from magnetic systems; the ω_{01}^3-dependence of the spontaneous emission clearly favors optical frequencies. The optical spectroscopic methods of fluorescence and phosphorescence are therefore mostly based on spontaneous emission processes. Similar experiments would be difficult, if not impossible, with ESR and NMR spectroscopy. Spin resonance experiments are, thus, based on coherent phenomena as described by the Bloch equations. Only after the advent of lasers as coherent light sources was it possible to perform coherent Bloch-type experiments in the optical region[48].
c) In optical spectroscopy the sample dimensions are, in general, large compared to the wavelength. In addition to the Bloch equations, Maxwell's equations therefore must also be applied. Both sets of equations are often referred to as the Bloch-Maxwell equations.
d) In magnetic resonance phenomena the Larmor frequency of the precessing spin ensemble has a geometric interpretation: The magnetization vector precesses, as long as it has a component perpendicular to the field direction, at the Larmor frequency. It can therefore be detected with appropriate detector coils which pick up an x−y magnetization. The "optical Larmor frequency" $\omega_{10} = (E_1 - E_0)/\hbar$ has no real geometric relevance, i.e. there is no precession in real x, y, z space.

In connection with the above considerations we wish to summarize the basic relations which link optical line width data with the corresponding optical relaxation times. The equations which will be given below can be derived by solving the time evolution of the density matrix of a two-level system driven by a coherent electric field, and represent the optical analogues of Bloch's equations for a precessing spin. They basically describe the phase decay of an ensemble of optically excited molecules (for a review see [49,50]).

If the pure dephasing time of the molecules is defined as T_2^* and the lifetime in the excited state as T_1, one arrives at an effective decay time of the total ensemble of excited molecules

$$1/T_2 = 1/T_1 + 2/T_2^* \tag{18}$$

In contrast to similar expressions derived in spin resonance spectroscopy, equation (18) is not symmetrical in T_1 and T_2^*. The reason for this difference is that for an optical two-level system the excited state cannot be populated thermally. This has as the consequence that only one of the two states (the excited one) can decay with T_1. Scattering processes with characteristic time T_2^* can, however, occur in both the ground and excited states.

Knowing T_1 and T_2, one can calculate the optical line width (FWHH; in units of 2π/s) of an optical two level system as

$$\gamma_h = \frac{1}{T_2}\sqrt{1 + \omega_1^2 T_1 T_2} \tag{19}$$

where ω_1 is the Rabi frequency, proportional to the amplitude of the electric field vector of the light wave. The characteristic time for driving the molecular ensemble from the

ground state to a state with equal population of the ground and excited states is $t=\pi/2\omega_1$; ω_1 is defined as

$$\omega_1=\vec{\mu}_{10}\vec{E}_0/\hbar \tag{20}$$

where $\vec{\mu}_{10}$ is the dipolar matrix element of the optical transition. Equation (19) shows that the optical line width increases at high light-intensities. This line-broadening is referred to as power broadening. In hole burning spectroscopy, one usually tries to avoid power broadening by performing the experiments at low power levels where the following condition holds

$$\omega_1^2 \ll \frac{1}{T_1 \cdot T_2} \tag{21}$$

These lower power levels require longer irradiation times for PHB photochemistry. It should be mentioned that the phenomenon of power broadening is completely different from the so-called "photochemical saturation broadening" (Section 9), which arises from bleaching of the photoactive molecules over a narrow frequency range.

As mentioned previously, excessively high light-intensities in hole burning experiments are avoided since power broadening would otherwise result. However, the methods used in transient spectroscopy, which are summarized in the following section, require high light-intensities. For these experiments equation (21) cannot be fulfilled, and the light field chosen has to be high enough to perform the transient changes in times small compared to T_1 and T_2^* (adiabatic rapid passage, see [51]).

6. Transient Experimental Methods for Determining Optical Relaxation Times

6.1. Free Induction Decay

A very useful method for measuring the optical relaxation time T_2 in the *time domain* is optical free induction decay (FID or OFID). In the FID experiment, a macroscopic polarization is generated in the sample by irradiating it with coherent light. The polarization field of the sample is then superimposed on the incident light field, leading to a beat frequency between the two oscillations. To observe FID experimentally, one has to "switch" the laser frequency fast (compared to T_1, T_2^*) into and out of the molecular resonance frequency. This can be achieved either by Stark-switching the molecular energy levels[52–54] or by rapidly switching the laser frequency[55].

The optimal experimental condition for observing FID arises if the polarization corresponds to equal population of the ground and excited states. This is achieved by irradiating a resonant field during the time interval $t_{\pi/2}$, thereby rotating the polarization by $\pi/2$. To achieve a $\pi/2$-rotation, the condition

$$\omega_1 \cdot t_{\pi/2}=\pi/2 \tag{22}$$

has to be fulfilled.

After generating the above polarization, the laser frequency is quickly shifted from ω_{01} to $\omega_{01}+\delta\omega$. It is important that $\delta\omega$ be several times larger than the homogeneous line width. In this case the beat phenomenon between the (complex) polarization $\vec{P}$ and the external field decays according to the following relation:

$$\vec{P}(t)=\vec{\mu}_{01} N \exp\{i\,\delta\omega\, t\} \cdot \exp\{-t/T_2\} \tag{23}$$

Equations (23) and (24) show no high frequency oscillations with ω_{01}, since they are formulated in a reference frame rotating at frequency ω_{01} (rotating frame description).

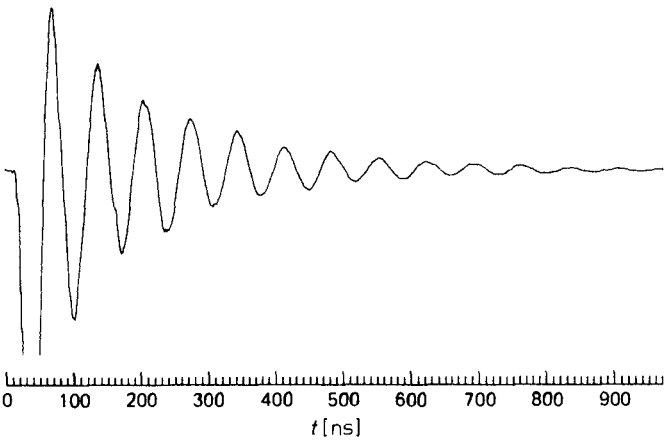


Fig. 10. Optical free induction decay (OFID) of the praseodymium(III) ion in lanthanum trifluoride [56].

In equation (23), N is the number of molecules in the ensemble and $\delta\omega$ is the beat frequency between the sample polarization and the light wave. Figure 10 shows an FID signal of an excited state of the praseodymium(III) ion in a lanthanum trifluoride crystal at 1.5 K. The rapid oscillations correspond to the frequency shift $\delta\omega$. The envelope of the signal corresponds to T_2[*].

6.2. Optical Echo Experiments

In Section 6.1 we assumed for the sake of simplicity that the molecular transitions are narrow (with a width of the order of $1/T_2$). In reality, the transitions are, however, *inhomogeneously* broadened. The time decay of the polarization after a $\pi/2$-pulse is, hence, not given by equation (23) but has to be rewritten (see e.g. [52]):

$$\vec{P}(t-t_{\pi/2})=\vec{\mu}_{01}\left[\sum_j^N \exp\{iD_j(t-t_{\pi/2})\}\right]\exp\{-(t-t_{\pi/2})/T_2\} \tag{24}$$

where D_j characterizes the shifts of the molecular frequencies with respect to the laser frequency caused by inhomogeneity effects [see eq. (17)]. The term in the square brackets of equation (24) decays quickly due to the different molecular frequencies involved. We interpret this decay graphically by describing the polarization vector after a $\pi/2$-pulse in a *fixed* coordinate system. In such a coordinate

[*] In the original paper [56] the envelope corresponds to $1/2\,T_2$, since effects due to the line inhomogeneity have to be taken into account. Inhomogeneity effects are, for simplicity, not included in equation (23) (see Section 6.2).

system the polarization rotates with the Larmor frequency ω_{01}. Ideally in the case of vanishing inhomogeneity, the ω_{01} frequency of all particles, i.e. molecules of the ensemble, is identical and, hence, the length of the polarization vector decays with time constant T_2. Figure 11a shows the situation for two different times τ and 2τ.

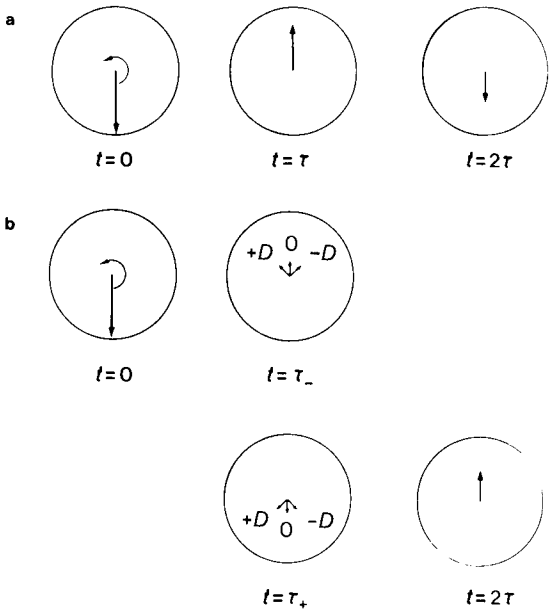


Fig. 11. a) Polarization decay (length of arrow) after a $\pi/2$-pulse. The arrow rotates at the Larmor frequency ω_{01}. The polarization executes $n+1/2$ rotations during the time interval τ and $2n+1$ during the time interval 2τ ($n=\omega_{01}\cdot t/2\pi$). The polarization decays exponentially with characteristic time T_2. b) In the presence of inhomogeneous broadening, the polarization decays faster. The polarization is symbolically composed of three different components: one with the unperturbed Larmor frequency (0) and a faster (D^+) and a slower (D^-) component. τ_- is the time immediately before and τ_+ the time immediately after the 180°-pulse. (The three arrows are all short due to the "spread out" from inhomogeneity.) After $2n+1$ rotations of the polarization the three components refocus and give rise to an echo. (The difference of half a rotation between a) and b) is due to the 180°-pulse.)

Due to the scattering of molecular frequencies in the range $\omega_{01} \pm D$ (inhomogeneous broadening), a decay of the polarization which is much faster than the "true" T_2-decay is also encountered. This is shown in Figure 11b for the time interval $0 \leq t \leq \tau$. For simplicity we consider only three frequency components: An unshifted component at ω_{01}, a fast component at $\omega_{01}+D$, and a slow component at $\omega_{01}-D$. If after a time τ a π-pulse is applied to the system, the slow and the fast components are interchanged as shown in Figure 11b, the slow component preceding the fast (a π-pulse corresponds to an inversion in the two-level system). If one follows the time evolution of the system after the π-pulse, the various Larmor components refocus at $t=2\tau$ and are shifted by 180° (Fig. 11a). The polarization which refocusses at $t=2\tau$ generates an optical echo, which can be detected in a similar way to the OFID signal. The π-pulse has the consequence that at $t=2\tau$ the interference term of equation (24) (square brackets) is equal to unity, as is shown graphically in Figure 11b for two discrete D_j values. Equation (25) describes the decay of the refocussed polarization function, which is measured in an echo experiment.

$$\tilde{P}(\pi/2,\pi,2\tau)=\vec{\mu}_{10}N\exp\{-2\tau/T_2\} \qquad (25)$$

The echo method was first introduced by *E. L. Hahn* in NMR spectroscopy[57]. The first optical echoes were measured in 1964 in ruby crystals[48] (for a survey see [58,49]).

7. Relaxation Spectroscopy in the Frequency Domain

In Section 6.2 we described methods of measuring relaxation times by transient methods in the time domain. With the aid of equation (12) relaxation times can also be measured in the frequency domain. Both methods have advantages and disadvantages and are, in many respects, complementary. In the following we summarize their main differences.

a) Experiments in the frequency domain are difficult to perform for long relaxation times because they require both high frequency resolution and high frequency stability. Practical limits at present are ca. 10^{-4} cm^{-1} (1 MHz)[59,60]. For long relaxation times, FID and echo methods are preferable.
b) Frequency domain experiments are easier at short relaxation times (5 ps $\triangleq$ 1 cm^{-1}). This favors their application to amorphous materials which have short relaxation times, i.e. glasses and polymers[43,45,61]. For these materials transient experiments have so far, with a few exceptions[62], failed. This was mainly due to difficulties in producing sufficiently rapid pulse sequences and high enough Rabi frequencies. At the very high laser powers required, sample heating is often a problem.
c) In contrast to transient experiments, frequency domain experiments can be performed with very low laser powers and are based on a photochemical process in which the sample accumulates the experimental information. Instead of performing an experiment over a short time span under high intensity conditions, the experiments can be extended over a longer time period with correspondingly lower laser intensities. This is principally important for low temperature experiments where sample heating has to be avoided.
d) Due to their advantages at very short relaxation times, frequency experiments are extremely useful for studies of phonon states, which are characterized by very short relaxation times[63,64].
e) A difficulty which arises with experiments in the frequency domain is the interpretation of the line shapes. Line shapes are not always Lorentzian as predicted by simple theories of relaxation. Spectral diffusion processes often have to be considered in addition to straight forward relaxation processes[65]. In the latter case the complementary use of time- and frequency-domain experiments is advantageous.

7.1. The Method of Fluorescence Line Narrowing

As mentioned in Section 4, in the solid state optical line widths are limited by inhomogeneity effects. Figure 9 shows symbolically that sites with different microstructures lead to line broadening. These broadening effects occur in both crystalline and amorphous materials; they are,

however, much more dominant for amorphous systems, leading to line widths of the order of several 100 cm^{-1}. The first investigations suppressing inhomogeneity effects were echo experiments on ruby performed by *Hartmann* et al.[48]. The first fluorescence line narrowing (FLN) experiments were also carried out on ruby by *Szabo*[66], who measured a homogeneous line width of 2×10^{-3} cm^{-1}. The FLN method was subsequently successfully applied to organic systems by *Personov* et al.[63] and to inorganic systems by *Riseberg*[67]. In the context of this article, we do not intend to give an exhaustive review of the FLN work; it is of relevance, however, that the optical spectroscopy of glasses has received new impulses through the introduction of FLN spectroscopy[63,67,68]. The advantage of the FLN method is its high resolution capability; its disadvantage is its off-resonance character. Usually one excites the 0-0 transition via laser stimulation and monitors the fluorescence of vibronic sidebands. Since the vibrational sidebands do not always have a full correlation with the 0-0 band, some line shape information is lost if only the sidebands are detected (see Section 12). Exceptions to these spectroscopic limitations are excited states with long lifetimes (phosphorescence line narrowing)[56,66,69]. In this case the optical spectrum can also be observed at the resonant laser frequency by gating methods (see dotted arrow in Fig. 12). In principle, this gating method can also be applied for short lived singlet states (10^{-8} s). Fast gating experiments are, however, difficult and to date the method has found no practical application.

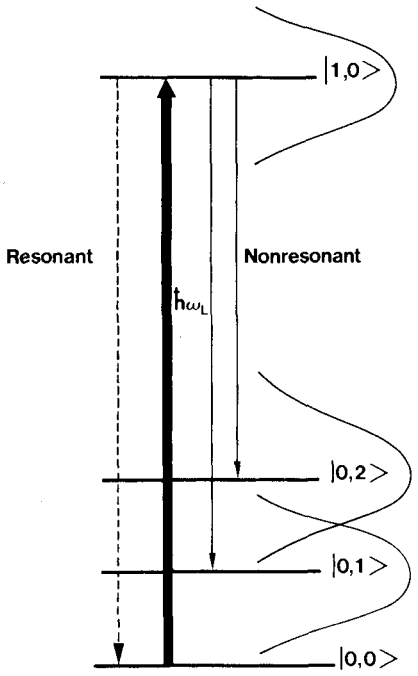


Fig. 12. Energy level scheme of a molecule with resonant and non-resonant fluorescence transitions. The symbol i,j characterizes the i-th electronic and the j-th vibrational level.

7.2. Spectral Hole Burning

The hole burning method was first introduced to NMR spectroscopy by *Bloembergen* et al.[70]. By saturating a two-level system, a hole can be "burned" in an inhomogeously broadened NMR line. The linewidth of the hole is, within a factor of two (vide infra), of the order of $1/T_2$.

Optical hole burning experiments were first performed in the gas phase[71]. The first experiment in the solid state was carried out on ruby by *Szabo*[72].

Transient NMR hole burning is a rather straightforward experiment because of the long T_1-times, which characterize the population decay following partial line saturation. A transient hole burning experiment has to be performed within a T_1-period, which, for nuclei, can be of the order of seconds to hours. Typical optical T_1-times for allowed optical transitions are of the order of 10^{-8} s; transient hole burning experiments in the optical domain are therefore difficult. *Szabo*'s experiment[72] was performed with a comparatively long-lived, forbidden transition in ruby (R_1 band).

Photochemical and *photophysical* hole burning experiments exhibit strong analogies to transient hole burning, but circumvent the difficulty which arises at short T_1-values. Figure 13 gives an extended two-level scheme characterizing both the photochemical and the photophysical experiments. Besides the states $|\Psi_0\rangle = |R\rangle$ and $|\Psi_1\rangle = |I\rangle$ discussed so far, one has to consider a photochemical product state $|P\rangle$ which is populated with quantum yield Φ. The absorption of n quanta transforms $n\Phi$ molecules into the photochemically or photophysically modified state $|P\rangle$. This process leads to a depletion of the ground-state and thus to a permanent hole in the absorption band, provided a back reaction from $|P\rangle$ to $|R\rangle$ is forbidden or infinitely slow. The first experiments on photochemical and photophysical hole burning were published in 1974 by *Rebane* and *Personov* and their respective groups[3,4]. The high resolution of the hole burning experiments was demonstrated two years later in 1976[73,74]. Applications of hole burning to the spectroscopy of glasses were first reported in 1976[42,46].

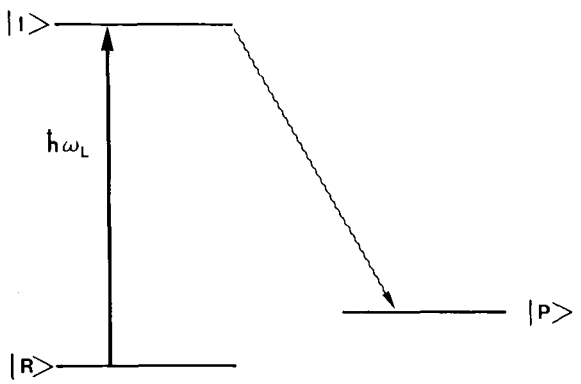


Fig. 13. Energy level scheme for the photochemistry of the hole burning process. $|R\rangle$ is the reactant state, $|P\rangle$ the product state, and $|I\rangle$ an intermediate state (for example the S_1 state).

With the aid of a few examples the difference between photochemical hole burning (PHB) and photophysical hole burning (non-photochemical hole burning, NPHB) will next be described.

In a typical PHB experiment the photoreactive molecules undergo photochemical changes, i.e. the absorption of the photoproduct is, in most cases, spectroscopically

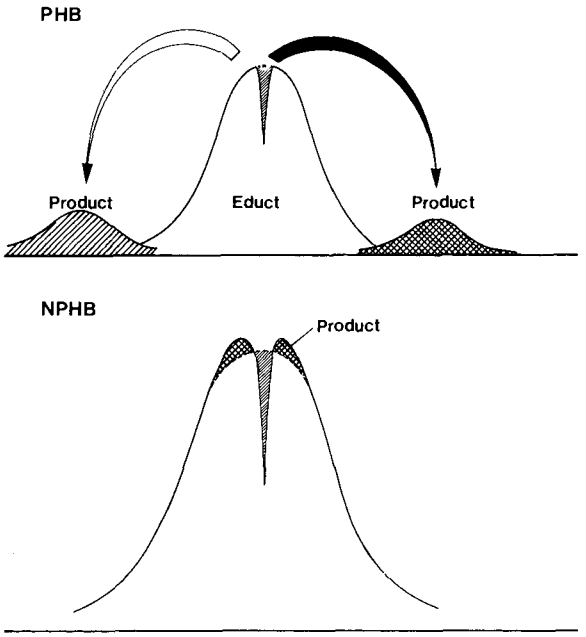
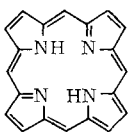
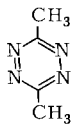
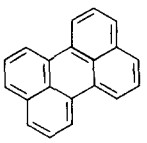


Fig. 14. Spectral distribution of the photoproduct after photochemical (PHB) and photophysical (NPHB) hole burning: The hole in the absorption band is clearly discernible.

well separated from that of the original absorption (educt). The new absorption can be both blue- and red-shifted (Fig. 14). Examples of reversible PHB processes are proton transfer in metal-free phthalocyanine and in porphin[74] or configurational changes of hydrogen bonds[61]. An example of irreversible PHB photochemistry with large photochromic shift is the two-photon photochemistry of dimethyl-*s*-tetrazine[73,75]. In the latter case, the molecule dissociates into fragments which absorb in the UV range of the spectrum. In all these cases a photoproduct $|P\rangle$ can be defined whose optical absorption is rather different from the spectrum of the pristine molecule. There are also photoactive systems at the border area between transient hole burning and photochemical hole burning; for example, color centers[60]. For such systems the "photochemistry" arises from a reversible, light-induced electron tunneling process. (The back-reaction in the dark usually has a time constant of the order of tens of minutes.)


Porphin


Dimethyl-*s*-tetrazine


Perylene

The NPHB method usually photochemically modifies the molecule-matrix interaction. As "photoactive" molecules usually species such as pyrene[4] or tetracene[43,46] are used, which, under normal conditions, are quite photostable. The light-induced changes of the optical properties depend, by definition, upon properties of the matrix. Matrices which form hydrogen bonds (e.g. ethanol-methanol glasses) seem to be suitable for this kind of photochemistry, whereas saturated hydrocarbons (e.g. *n*-alkanes) seem to be inapt for appropriate host-guest rearrangements. A spectroscopic selection criterion which distinguishes photochemical and photophysical hole burning processes is the position of the absorption of the photoproduct, which for the latter lies very close to the energy of the laser performing the site selection[43]. Therefore, the physical variant can be interpreted as a process which redistributes molecular absorbers within the inhomogeneous band profile. On a microscopic basis this can be envisaged as a process which changes a given molecule-matrix configuration into another which absorbs at a different frequency. Recently NPHB processes have also been observed in amorphous aromatic guest-host systems[76] (see Section 13). It should, finally, be mentioned that NPHB processes have also been observed in the IR spectral range (≈ 1000 cm^{-1})[77].

8. Photochemical Hole Burning: Mechanistic Aspects

In this section we discuss various basic mechanistic aspects underlying hole burning photochemistry. We argue that hole burning photochemistry is a special kind of photochemistry, fulfilling the criterion of "zero-phonon photochemistry"[61]; the latter criterion eliminates many known photochromic systems as good candidates for hole burning.

In Section 2 we discussed the criterion for the appearance of narrow zero-phonon lines in considerable detail, and saw that weak electron-phonon coupling (i.e. small S-values) was the main condition for observing intense zero-phonon lines [(eq. (8)]. A necessary condition for weak phonon coupling was a small change of the equilibrium configuration (q_{i0}) of the lattice in the excited state. Photoreactive molecules, however, are characterized by large changes of their molecular geometry along a reaction coordinate Q (Fig. 15a)[*]. These large changes in the reaction coordinate lead to large changes in the equilibrium positions of the lattice q_{i0}.

In general, photoreactive molecules therefore show strong electron-phonon coupling. The spectra of photoreactive molecules are therefore, on the whole, characterized by broad spectral bands and large Stokes-shifts. Arguments along these lines led to the postulate of proton-transfer processes in the excited state from an analysis of the corresponding molecular spectra[78,79].

From these arguments one can conclude that PHB processes require the existence of mutually exclusive conditions; namely photoreactivity on the one hand and sharp spectral lines on the other. However, for two photochemical reaction schemes, under which most known photoreactions can be categorized, both criteria are fulfilled simultaneously. Figure 15b shows what is termed "*slow photochemistry*". In this case the photoreactive state is not the site-selected state itself, but a third state. This state is mostly populated via radiationless transitions; it can be a triplet state (level crossing in Fig. 15b). The proton-transfer

[*] Q denotes an internal molecular coordinate, whereas q is used throughout this article to denote lattice coordinates.

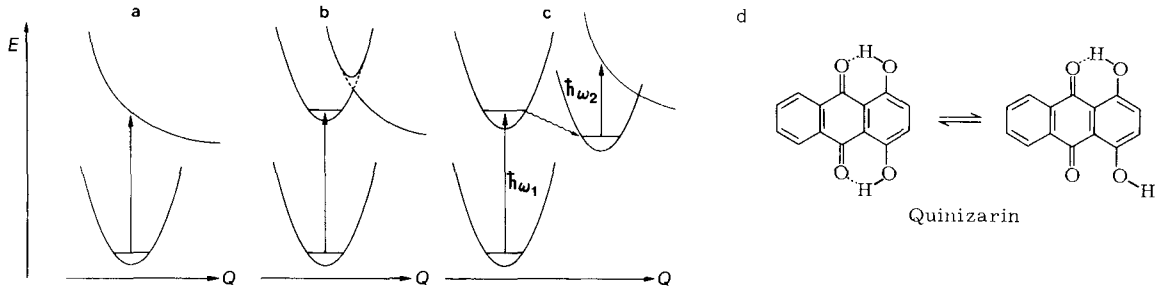


Fig. 15. a)—c) Photochemical model based on a configuration coordinate description of the photochemical process (see text). Q symbolizes an intramolecular coordinate. d) Reaction scheme for the proton transfer in quinizarin.

photochemistry of quinizarin (Fig. 15d) and the photochemistry of H_2-phthalocyanine and -porphin fall into this category. Even photophysical hole burning (NPHB) can be subsumed under this category. In the latter case it seems that the photochemical product state is reached via tunneling processes (see Section 13).

A second possible scheme is based on a *two-photon process*, as observed in the case of dimethyl-*s*-tetrazine[80]. Here, the first photon makes a site-selective transition into a photochemically inactive state, which undergoes relaxation to an intermediate state. The subsequent absorption of a second photon leads to a reactive state which initiates the photochemistry. The intermediate state has to be long-lived to achieve an acceptable quantum yield. Its spectroscopic properties are irrelevant for the hole burning process, whose site selection mechanism occurs during the transition $\Psi_1 \leftarrow \Psi_0$. Figure 15c shows the reaction scheme for a two-photon process[81]. In general, two-photon processes are desirable for technical applications such as optical memories and holographic photochemical applications. The technical advantage is that the first photon acts as a sensitizer, whereas the second photon initiates the irreversible information storage processes (see Section 15).

An important aspect of PHB photochemistry is the role played by the host lattice, which can, for example, cause activation barriers on the energy surfaces, thereby stabilizing various photochemical states[82]. Hence, at low temperatures, certain photochemical pathways may be inaccessible due to activation barriers which cannot be overcome by thermal energy. Such a case has been investigated using the dye molecule quinizarin as the photoreactive system[83]. The molecule undergoes light-induced proton transfer in which an intramolecular hydrogen bond can be opened or closed, depending on the wavelength of irradiation. The experimental results for the back transfer reaction of the proton indicate that the reaction can only occur in an excited phonon state of the lattice. The phonon excitations provide the energy to overcome the barrier of several 10 cm^{-1}, as shown in Figure 16. It should be noted that the phonon excitations needed to overcome the reaction barrier are "automatically" provided by Franck-Condon excitation of molecule-lattice states, as long as the molecule exhibits reasonably strong electron-phonon coupling. The forward reaction in which the hydrogen bond is opened is believed to occur via a low lying triplet state. We are not aware of any other examples of "phonon selective" photochemical reactions at low temperatures; however, no systematic studies of photochemical reactions have been performed at very low temperatures.

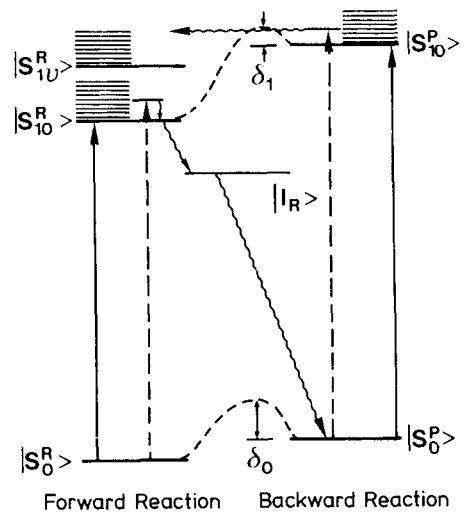


Fig. 16. Energy level scheme for the photoreactive state of quinizarin. $|I_R\rangle$ is a state of a reactive intermediate (most likely triplet); δ_0 and δ_1 symbolize reaction barriers in the ground and excited states, respectively.

9. Model Calculations of Photochemical Hole Burning in Organic Glasses

9.1. Line Shape Equations for Photochemical Hole Spectra

The three-level system shown in Figure 13 accounts for many characteristic features of the hole burning process: The photochemical process leads from the initial state $|R\rangle$ via an intermediate state $|I\rangle$ to the final photoproduct state $|P\rangle$. The excitation energies $\hbar\omega'$ of the initial state are scattered around a center of energy $\hbar\omega_0$ with the width Γ, due to a variation of the D values about D_0 [eq. (17)]:

$$\frac{N(\omega')}{N_0} \equiv \rho(\omega') = 2\sqrt{\frac{\ln 2}{\pi}} \cdot \frac{1}{\Gamma} \exp\left\{-\frac{4(\omega'-\omega_0)^2 \ln 2}{\Gamma^2}\right\} \tag{26}$$

$N(\omega')/N_0$ is the fraction of molecules which absorb in the frequency interval $d\omega'$ centered at ω'. In order to calculate the PHB line shape, the number of molecules at ω' after laser irradiation at ω_L must first be calculated.

It is important to note that a molecule which is centered at ω' absorbs at the laser frequency ω_L via two different processes: through the wings of its zero-phonon line z and through its phonon sideband p (Figs. 17 and 4). The transi-

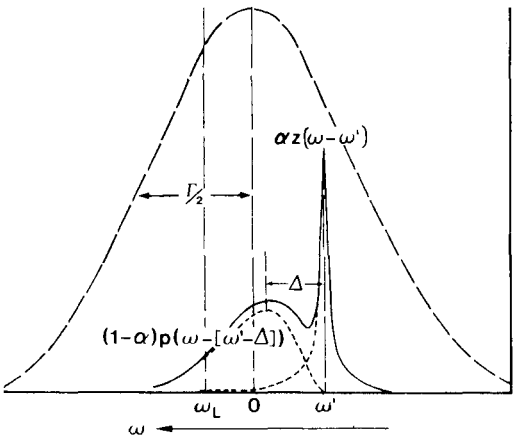


Fig. 17. Inhomogeneous distribution with a half width of Γ (full width at half height; FWHH) and spectral line shape profile of a molecule absorbing at frequency ω': z is the zero-phonon line, p the phonon sideband, ω_L: laser frequency. α: Debye-Waller factor. Δ: half the Stokes-shift. (The zero of the frequency scale corresponds to the frequency ω_0.)

tion probability per time unit can therefore be expressed as the sum of two terms

$$W(\omega_L,\omega') = \frac{\sigma I}{\hbar\omega_L}\{\alpha z(\omega_L-\omega') + (1-\alpha)p(\omega_L-\omega'-\Delta)\} \quad (27)$$

where σ is the absorption cross-section integrated over the frequency space, and $I/\hbar\omega_L$ is the number of incident photons per unit time and unit area. If Φ is the photochemical quantum yield, the change in the relative number of molecules $d\rho$ per time unit dt is given by

$$d\rho = \rho(\omega')\Phi\, W(\omega_L,\omega')\, dt$$

After integration we obtain

$$\rho_\tau(\omega') = \rho_0(\omega')\exp\{-W(\omega_L,\omega')\Phi\cdot\tau\} \quad (28)$$

where τ is the burning time.

A convolution of ρ_τ and the line profile $\alpha z(\omega-\omega') + (1-\alpha)p(\omega-\omega'-\Delta)$ affords the photochemically modified absorption spectrum $A_\tau(\omega)$.

$$A_\tau(\omega) = \sigma \int_{-\infty}^{+\infty} \rho_\tau(\omega')\{\alpha z(\omega-\omega') + (1-\alpha)p(\omega-\omega'-\Delta)\}\, d\omega' \quad (29)$$

The difference $A_0(\omega) - A_\tau(\omega)$ describes the photochemical change in the spectrum, which we refer to as photochemical hole spectrum $L_\tau(\omega)$:

$$L_\tau(\omega) \equiv A_0 - A_\tau = A_0(\omega) - \sigma \int_{-\infty}^{+\infty} \rho_0(\omega')\exp\left\{-\sigma\cdot\Phi\frac{I}{\hbar\omega_L}\tau[\alpha z(\omega_L-\omega') + (1-\alpha)p(\omega_L-\omega'-\Delta)]\right\}\{\alpha z(\omega-\omega') + (1-\alpha)p(\omega-\omega'-\Delta)\}\, d\omega' \quad (30)$$

Since z is a function which is narrow compared to ρ and p, eq. (30) can be resolved into four terms which permit a quite straightforward interpretation (Fig. 18)[84]:

$$zz(\omega) = \sigma\alpha\rho_0(\omega_L)\left\{1 - \int_{-\infty}^{+\infty}\exp\left\{-\frac{\alpha\sigma I\Phi\tau}{\hbar\omega_L}z(\omega_L-\omega')\right\} z(\omega-\omega')\, d\omega'\right\} \quad (31)$$

where $zz(\omega)$ is the narrow zero-phonon hole, whose shape depends on experimental parameters such as laser intensity I and burning time τ.

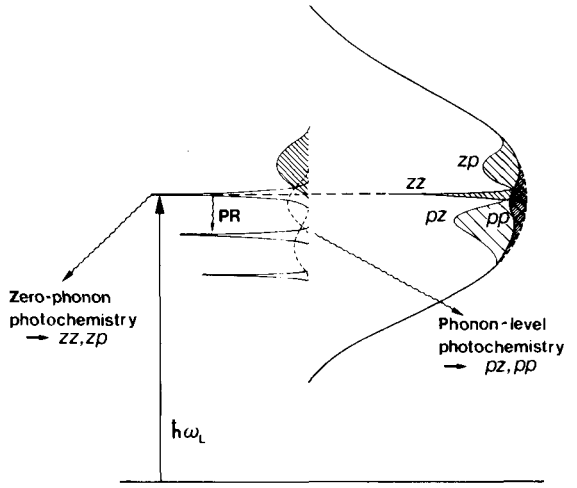


Fig. 18. Graphical scheme representing the four contributions to a photochemically burned hole zz, zp, pz, and pp. PR: phonon relaxation (see text).

The molecules whose electronic energy is centered at the zero-phonon line $zz(\omega)$ give rise to a phonon sideband absorption, which in turn gives rise to a broad hole on the short wavelength side of the zero-phonon hole. This broad hole is called the direct phonon sidehole, because it is a true satellite of the zero-phonon line:

$$zp(\omega) = \sigma(1-\alpha)p(\omega-\omega_L-\Delta)\cdot N_z(I,\tau) \quad (32)$$

The line shape of zp is determined solely by the phonon spectrum p. $N_z(I,\tau)$ is the relative number of molecules which have been changed photochemically by zero-phonon absorption:

$$N_z(I,\tau) = \rho_0(\omega_L)\left\{1-\exp\left[\frac{-\sigma\alpha I\Phi\tau}{\hbar\omega_L\gamma_h}\right]\right\}\gamma_h \quad (33)$$

$N_z(I,\tau)$ is proportional to the homogeneous line width γ_h. The exponent in equation (33) defines a bleaching time τ_b for the zero-phonon line[84]:

$$\tau_B = \gamma_h \Big/ \frac{I\Phi\alpha\sigma}{\hbar\omega_L} \quad (34)$$

τ_b is rather short for low temperatures (≈ 1 K), since γ_h is small. It should, however, be noted that γ_h may increase rapidly with increasing temperature (see Section 10).

Figure 18 shows that in addition to molecules absorbing in their zero-phonon lines, one has to consider molecules with electronic energies lower than $\hbar\omega_L$. These absorb at the laser frequency via their phonon sidebands. This process creates a broad hole at energies lower than $\hbar\omega_L$, which is basically characterized by the line shape of the phonon sideband

$$pz(\omega)=\sigma\alpha\rho_0(\omega)\left\{1-\exp\left[-\sigma(1-\alpha)\frac{I}{\hbar\omega_L}\Phi\tau p(\omega_L-\omega-\Delta)\right]\right\} \quad (35)$$

where $pz(\omega)$ depends on the parameters I and τ used in the experiment. This dependency causes a strong asymmetry in the hole burning line shape as the total light dose $I\cdot\tau$ increases (Fig. 19). We call $pz(\omega)$ a *pseudo-phonon hole,* since

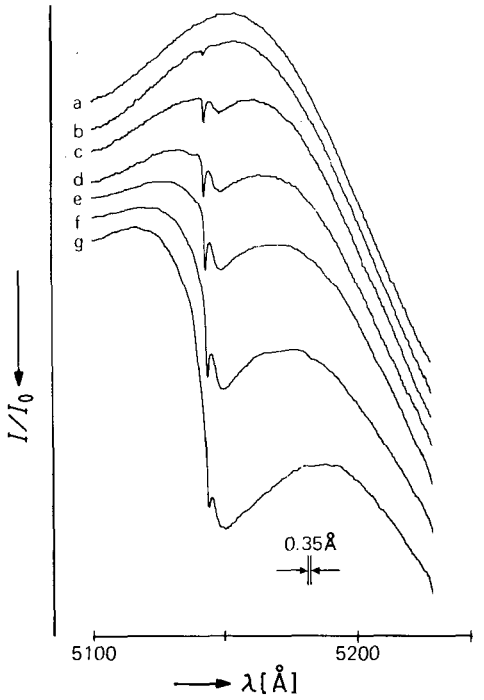


Fig. 19. Growth of a photochemical hole as a function of integrated irradiation time. Quinizarin in ethanol-methanol glass (3 : 1). a) Spectrum prior to irradiation, b) after 1 s, c) after 6 s, d) after 16 s, e) after 1 min, f) after 5 min, and g) after 32 min irradiation time (Argon ion laser, 7 mW/cm^2; T = 1.8 K).

this term does not represent a real phonon sideband belonging to a zero-phonon origin (it is rather a convolution of zero-phonon lines). Finally, the molecules which constitute the pseudo-phonon hole have their own phonon wings. This gives rise to a phonon-phonon term:

$$pp(\omega)=\sigma(1-\alpha)\int_{-\infty}^{+\infty}\rho_0(\omega')\left\{1-\exp\left[-\frac{\sigma I}{\hbar\omega_L}\Phi\tau(1-\alpha)p(\omega_L-\omega'-\Delta)\right]\right\}p(\omega-\omega'-\Delta)\,d\omega' \quad (36)$$

Whereas zp is on the short wavelength side of ω_L and pz is on its long wavelength side, pp has contributions on both sides of ω_L and, for low radiation dose, is symmetric with respect to ω_L (see Section 9.2). For small electron-phonon couplings pp is of minor importance, since the small quantity $(1-\alpha)$ appears both in front of the integral and in the exponent of equation (36).

9.2. Limiting Cases: Short Burning Time Limit

If the burning time τ is considerably shorter than τ_b, the exponent of equation (31) can be expanded into a power series. Neglecting higher terms, the line shape of the zero-phonon hole can then be written as

$$zz(\omega)=\frac{I\cdot\tau}{\hbar\omega_L}\sigma^2\alpha^2\Phi\rho_0(\omega_L)\int_{-\infty}^{+\infty}z(\omega_L-\omega')z(\omega-\omega')\,d\omega';\ \tau\ll\tau_b \quad (37)$$

For most practical cases, $z(\omega)$ is Lorentzian

$$z(\omega)=\frac{\gamma_h}{2\pi}\frac{1}{(\omega-\omega')^2+\gamma_h^2/4} \quad (38)$$

In this case the convolution integral [eq. (37)] can be solved, giving

$$zz(\omega)=\frac{I\cdot\tau}{\hbar\omega_L}\sigma^2\alpha^2\Phi\rho_0(\omega_L)\frac{\gamma_h}{\pi}\frac{1}{(\omega-\omega_L)^2+\gamma_h^2} \quad (39)$$

Equation (39) is also characterized by a Lorentzian line shape; however, with a line width of $2\gamma_h$. The short burning time limit enables one to interpret line widths in terms of the pertinent relaxation times. Equation (37) further predicts a linear growth of the zero-phonon hole with irradiation time τ.

From equations (35) and (36) it can also be concluded that for $\tau\ll\tau_b$ the pseudo-phonon hole and the direct phonon hole have identical shape and depth. $L_\tau(\omega)$ is therefore completely symmetric with respect to the laser frequency ω_L[64].

9.3. Limiting Cases: Photochemical Saturation Limit

With increasing irradiation dose $I\cdot\tau$, photochemical reactions at the center of the line gradually come to a halt because most photoactive molecules have already been converted. Consequently, photochemical reactions shift increasingly to the wings of the line leading to a line broadening, termed photochemical saturation broadening (see Section 9.4). For $\tau\gg\tau_b$, the term N_z in equation (33) does not increase much. In the range of the pseudo-phonon hole, however, the photochemical reactions still progress. This is because many more molecules absorb in the area of the broad pseudo-phonon wing compared to the narrow range of the zero-phonon hole.

The hole spectrum therefore shows a non-linear growth rate (Fig. 19). These considerations make it evident that for a determination of α it is not sufficient to measure the relative intensity of the zero-phonon hole given by equation (7). Instead, a complete computer simulation has to be performed[64]. Only for times $\tau\ll\tau_b$ is the relative area of the zero-phonon hole given by α^2.

9.4. Hole Width and Laser Burning Time

The line width of the zero-phonon hole as a function of τ (or I) can be calculated analytically only for the limiting cases $\tau\ll\tau_b$ and $\tau\gg\tau_b$ using equation (31). As $\tau\to0$, the line width approaches $2\gamma_h$ linearly[85]. For $\tau\gg\tau_b$ the exponen-

tial factor in equation (31) can be omitted from the integral, since it is a function which varies slowly with ω due to photochemical saturation (slow compared to z). Using this approximation, the hole width can be calculated as:

$$\gamma(\tau) = \sqrt{\frac{\alpha\sigma\Phi\gamma_h}{\pi \ln 2 \hbar\omega_L} I\cdot\tau} \qquad (40)$$

The hole width increases with the square root of $I\cdot\tau$. Figure 20 shows a computer simulation of a typical saturation curve[86].

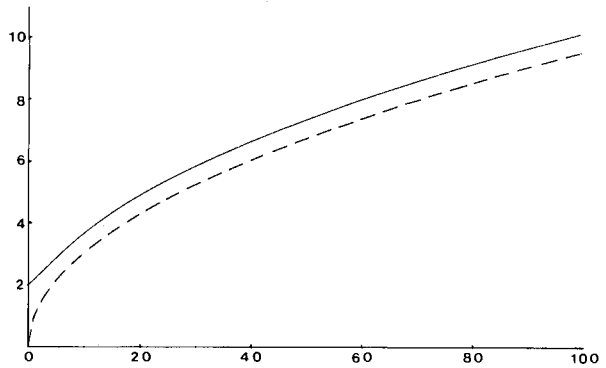


Fig. 20. Computer simulation of a photochemical bleaching curve [86] according to equation (31). Abscissa: Burning time in units of τ_b. Ordinate: Hole width in units of γ_h. The dotted line represents the asymptotic case according to equation (40).

9.5. Temperature Effects on the Emission Spectra of Photoreactive Molecules

At very low temperatures the emission spectra of photoreactive molecules in glasses exhibit a rather strange temperature behavior. In contrast to what one would expect, they do not exhibit narrow zero-phonon lines but show, instead, only broad spectra typical of phonon sidebands (Fig. 21a). At higher temperatures, however, narrow lines appear in the spectra (Fig. 21b). This rather unexpected phenomenon can be explained as follows: At low temperatures the short bleaching times lead to a rapid disappearance of molecules which absorb and emit at the laser frequency. The remaining nonresonant molecules give rise to the observed broad structures. With increasing temperatures, the bleaching time of the zero-phonon lines increases [eq. (34)] and, hence, the resonantly absorbing molecules appear in the spectrum[84]. This unconventional temperature dependence of the observed narrow zero-phonon lines is due to the bleaching effect of the photochemical system which may occur in the time scale of minutes up to several tens of minutes and, hence, may modify the observed fluorescence spectra.

9.6. Limits of the Model and Further Developments

The model which has been presented above makes assumptions which may, in some instances, not be valid. We have, for example, neglected all non-linear effects in the interaction between molecules and the laser field. This seems to be justified, if CW-lasers which operate in the

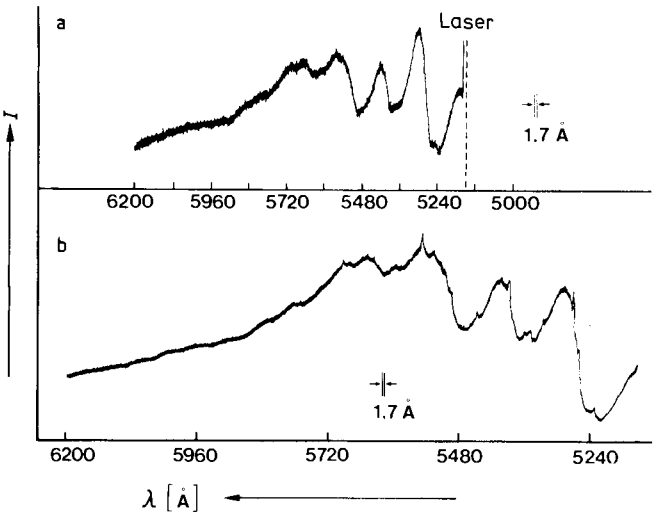


Fig. 21. Emission spectrum of quinizarin in an ethanol-methanol glass (3 : 1) at a) 1.8 K and b) 20 K. Excitation: Argon ion laser, 5145 Å, 7 mW/cm^2 [84].

mW range are used and if one investigates organic molecules in glasses which are characterized by comparatively large line widths. If, however, crystalline systems are studied using pulsed lasers, the non-linear effects may be of importance and have to be included in the theoretical treatment[87,88]. We have further assumed that no states with long lifetimes (e.g. triplet states) are involved in the photochemical cycle. Long-lived triplet states can, for example, give rise to bottlenecks and lead to accumulation of a large fraction of the molecules, thus causing non-linearities[87]. A similar effect can arise from the photochemical equilibrium between the states $|R\rangle$ and $|P\rangle$[5,88] (Fig. 13). Finally, one has to consider tunneling processes in glasses (Section 13), which can occur in the ground state and which can lead to spectral diffusion[65]. This latter effect has not been investigated yet in sufficient detail; however, it seems to have a considerable influence on the measured line widths.

Finally, it must be taken into account that in glasses all physical parameters, such as α, Φ and γ_h, are not characterized by a single, well-defined value, but by distribution functions. In consequence, the measured results may depend on the time-scale of the experiment[64].

10. Experimental Determination of Relaxation Processes in the Frequency Domain

Even in the early stages of photochemical hole burning, workers were aware of the possibility of determining relaxation times[5,73] from measurements of homogeneous line widths as defined by equations (12) and (19). By choosing appropriate experimental conditions, one can select the external parameters such that the following conditions hold

a) $1/T_2^* \ll 1/2T_1$ or b) $1/T_2^* \gg 1/2T_1$

Case a) is, for example, frequently fulfilled if the resonant state is a vibrational state. In experiments conducted using crystals at 4 K, the vibrational relaxations are, in general,

much shorter than the pure dephasing times and hence, vibrational relaxation times can be measured down to the sub-picosecond range. Systematic experiments for various vibrational levels have been published for porphin in *n*-alkane matrices[89]. Figure 22 shows that there is no straightforward relation correlating the relaxation times with the vibrational energies. The measured relaxation times vary over the range 1 to 40 ps. More recent experiments have shown that the vibrational relaxation in porphin strongly depends on the host matrix and on the local molecular environment[90]. Besides the experimental determination of vibrational relaxation times, the relaxation times of purely electronic transitions can also be measured[59,74,91]. These experiments are more difficult, since the relaxation times involved are comparatively long and, hence, the line widths quite narrow. The laser stability required, therefore, has to be better than 10 MHz ($=3\times10^{-4}$ cm^{-1}). In most crystalline systems the line width at 2 K is limited by the lifetime of the excited state [eq. (10)]. (The situation is more complicated in the case of glasses, since the underlying physics is rather complex (see Section 13).) If the temperature is raised, the line width increases rapidly and one approaches the range b), in which the line width is determined by pure T_2^*-dephasing processes.

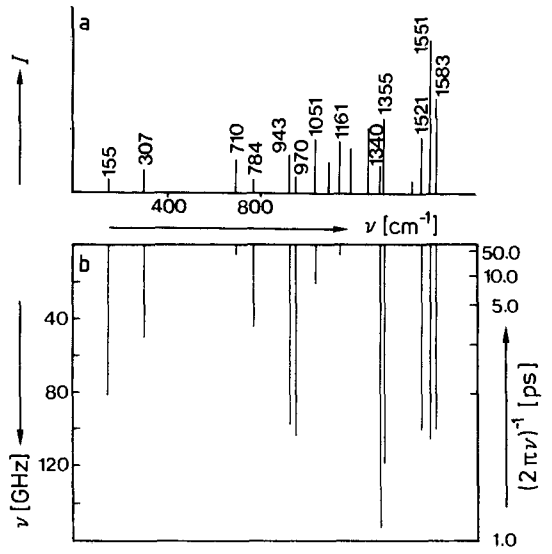


Fig. 22. Line widths of various vibronic states of porphin in *n*-octane [89]. a) Schematic excitation spectrum; b) corresponding line widths. *ν*: Frequency offset from the origin.

As discussed qualitatively in Section 3, phase relaxation is due to elastic phonon scattering processes in the various electronic levels. If these scattering processes are caused by the entire Debye phonon-spectrum (non-resonant scattering), then, well below the Debye temperature Θ, the line width follows a power law proportional to T^7:

$$\gamma_h(T)-\gamma_h(0)=\gamma_2\left(\frac{T}{\Theta}\right)^7 \tag{41}$$

Above the Debye temperature this power law changes to a quadratic law; γ_2 is a constant and is not a function of temperature (see [23]).

If the scattering processes are mainly due to a single, localized phonon state of frequency ω_0 (such as, e.g., a libration of the molecule), it can be shown that the temperature-dependence of the linewidth γ_h is given by the thermal occupation number of the pertinent phonon state, leading to the following relation:

$$\gamma_h(T)-\gamma_h(0)=\gamma_2'\langle n(\omega_0)\rangle(\langle n(\omega_0)\rangle+1) \tag{42}$$

where $\langle n\rangle$ is given by equation (13). In this case one speaks of resonant phonon scattering. For $\hbar\omega_0 \ll kT$, equation (42) leads, to a good approximation, to a quadratic temperature dependence. For $\hbar\omega_0 \gg kT$, one can extrapolate to an exponential behavior $\exp(-\hbar\omega_0/kT)$[74,92].

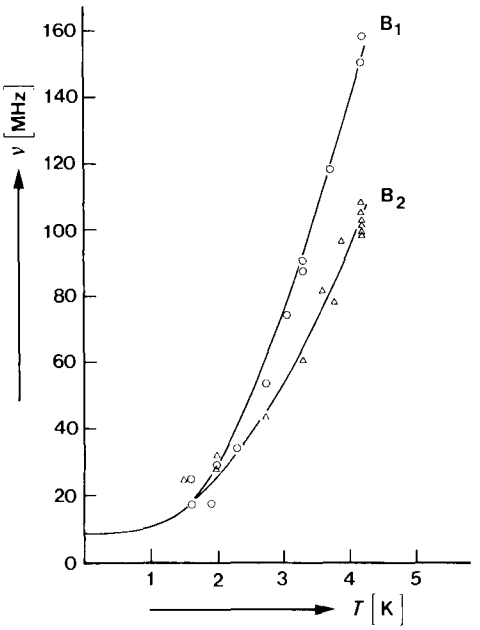


Fig. 23. Temperature dependence of the homogeneous line width of porphin in *n*-octane for the B_1- and B_2-sites [74].

Figure 23 shows the homogeneous line width of porphin in *n*-octane as a function of temperature[74]. The theoretical curves are calculated using equation (42). As $T\rightarrow0$, the line width approaches the limiting value of 9 MHz. This corresponds to the "Heisenberg limit", in which the line width is given by the fluorescence lifetime.

The influence of local lattice vibrations can also be interpreted within the framework of the theory of the optical exchange mechanism[59,93,94]. Figure 24 shows the main features of the model: The optical transition between the two phonon levels shows an energy mismatch Δ with the purely electronic transition. Since the phonon states are, in thermal equilibrium, constantly created and annihilated, the optical line constantly jumps between the two transition frequencies ω and $\omega+\Delta$. This leads to a broadening which for low temperatures ($\hbar\omega_0 \gg kT$) is given by

$$\gamma_h(T)-\gamma_h(0)=2\Delta\tau\frac{\Delta}{1+\Delta^2\tau^2}\exp(-\hbar\omega_0/kT) \tag{43}$$

where τ is the lifetime of the excited phonon state. A characteristic feature of the model is the frequency shift as a function of temperature, which is given by:

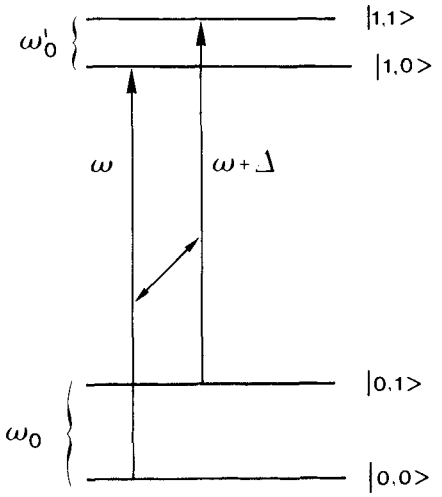


Fig. 24. Four-level scheme on which the optical exchange narrowing model is based (see text).

$$\omega(T)-\omega(0)=\frac{\Delta}{1+\Delta^2\tau^2}\exp(-\hbar\omega_0/kT) \tag{44}$$

Three cases can be distinguished[94]:

Fast exchange: $\Delta\cdot\tau\ll 1$
Slow exchange: $\Delta\cdot\tau\gg 1$
Intermediate exchange: $\Delta\cdot\tau\approx 1$

By measuring both the frequency shift and the line broadening as a function of temperature, one can determine the quantities Δ and τ as well as the energy of the associated phonon state. For porphin in *n*-octane the phonon energy was found to be 15 cm^{-1}; its lifetime was estimated to be 3 ps.

In the slow exchange limit the frequency shift is very small, and $\gamma_h(T)$ is independent of Δ[95].

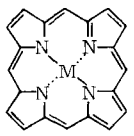
In equations (43) and (44) τ is assumed to be independent of temperature. This assumption may be valid for phonons over a narrow temperature range. Since, however, the exchange can also occur with states other than those of phonons (e.g. TLS), τ can become temperature dependent. In this case, situations in which $\gamma_h(T)$ increases with increasing temperature and those in which it decreases with increasing temperature (optical exchange narrowing; see Section 13) can be encountered.

11. Photochemical Holes in External Fields

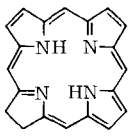
Due to their narrow width, photochemical holes can be regarded as excellent frequency markers which allow one to measure spectral changes of the order of a line width. These small changes would remain undetected, if one were to measure the complete broad inhomogeneous band. Hence, hole burning can be used to increase the experimental accuracy of measured line shifts by several orders of magnitude. This has been used for to measure small Zeeman and Stark shifts in doped crystals and glasses.

11.1. Zeeman Experiments

Zeeman studies of optical transitions of organic molecules were conducted in 1971 using metal porphinates[96]. These molecules have D_{4h} point group symmetry; their S_1-state is characterized by an electronic angular momentum perpendicular to the molecular plane (z-axis), which gives rise to a magnetic moment in the S_1-state. The twofold degeneracy of the S_1-state is removed in the crystal field,



Metal(II)-porphinate



Chlorin

leading to a small splitting. Due to the small splitting, the interaction between the two crystal field states is comparatively large and, therefore, the energy shift ΔE in an external magnetic field is, in case of the S_1-state, larger than the inhomogeneous band width. This large energy difference can readily be detected and allows the determination of the matrix element Λ characterizing the angular momentum:

$$\Delta E=-(\beta\Lambda H_z)^2/(E_2-E_1) \tag{45}$$

$$\Lambda=|\langle S_1|L_z|S_2\rangle| \tag{46}$$

Typical Λ values range between 4.2 and 4.3. Λ is an interesting quantity, because it can be calculated within the framework of structural models. Comparison with experimental data permits a convenient examination of the validity of the molecular models.

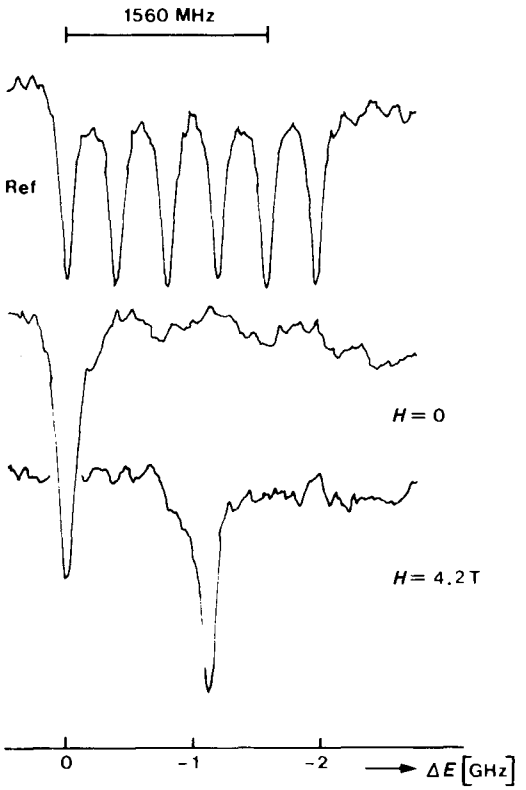


Fig. 25. Zeeman shift of a photochemical hole of porphin in *n*-octane [97] (see text).

These experiments are not feasible with the free base porphin. Because the molecular symmetry is lowered from D_{4h} to D_{2h} the two levels, which were originally split by the crystal field, are now split by the molecular field and are ca. 3000 cm^{-1} apart. Equation (45) shows that the Zeeman-shift is inversely proportional to the energy splitting and, thus, one can expect Zeeman-shifts of 0.03 cm^{-1}, which is about 1/30th of the inhomogeneous line width Γ (Γ in n-alkane crystals is ca. 1 cm^{-1}). Nevertheless, by applying PHB methods it was possible to determine the Zeeman shift[97]. Figure 25 shows the results obtained using two identical samples at 2 K. One of the samples was in a superconducting coil; the other sample was used as a reference wavelength marker into which a series of holes was burnt, which were separated by the laser modes. The "master sample" had only one hole, whose shift with external magnetic field could be measured by comparing it with the hole pattern of the reference sample. Using this high precision method, it could be shown that the Λ-value is much larger for free base porphin relative to those of metal porphins. With the same method one could also perform Zeeman experiments using the two tautomers of chlorin (7,8-dihydroporphin)[98,99]. By comparison of the corresponding Zeeman-shifts in the various "sites" of the *n*-alkane crystal the energy difference E_2-E_1 and Λ for both tautomers could be determined.

Transient optical hole burning experiments were performed using inorganic crystals. Since these crystals do not exhibit "permanent" photochemical states for the hole burning experiment, their nuclear hyperfine states were used as long-lived "hole states", marking the shifts by external fields[100,101]. If hyperfine states are used one can utilize holes as probes for RF-transitions in the spin systems and develop rather sophisticated techniques [optical detection of nuclear magnetic resonance (ODNMR) and optical detection of nuclear quadrupole resonance (ODNQR)].

11.2. Stark Experiments

Similar techniques can be used to study molecular interactions with external electric fields with vastly increased precision. Molecules without centers of inversion possess a permanent dipole moment and, hence, their transition energy changes linearly in an external electric field (linear Stark-shift). Symmetric molecules without permanent dipole moments exhibit a quadratic Stark-shift.

By evaluating these shifts, small changes in the dipole moment and in the polarizability upon electronic excitation can be measured. Frequently these methods also give some insight into the relative orientation between the guest molecule and the host crystal. Figure 26 shows the results of a Stark experiment with chlorin[102]: The hole observed exhibits splitting in an external electric field due to the inversion symmetry of the crystal. Whereas the dipole moment of chlorin only changes its absolute value (0.23 D), its photo-isomer also changes its direction. The directional change of the isomer is also "site dependent", presumably because of the strong S_1, S_2 mixing which occurs due to the small S_1-S_2 energy gap.

A combination of spectral hole burning and Stark effect has also been applied to color centers in NaF[103-105]. The

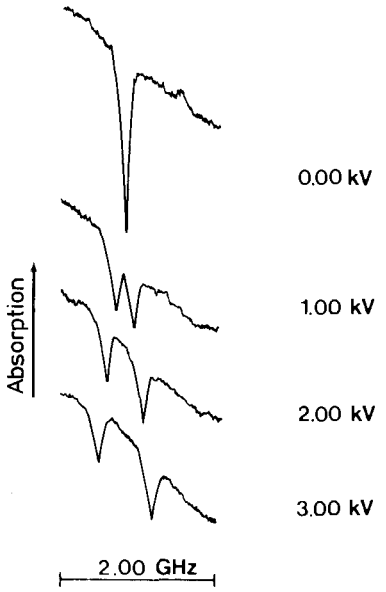
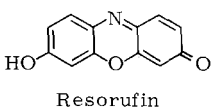


Fig. 26. Stark-shift of a photochemical hole of chlorin in *n*-hexane [102] (see text).

hole burning mechanism presumably involves either photo-ionization or electron tunneling in the excited state. The observed lifetimes of the corresponding photoproducts can be rather long (back tunneling to the original state). Stark experiments allow conclusions to be drawn which clarify both the symmetry and microscopic nature of the corresponding color centers.

Stark experiments in glasses are rather different from those in single crystals. Here, the external field leads mainly to broadening of the observed holes due to the geometry of the isotropic glass. From the increase in line width, the average changes in the electric (or magnetic) dipole moment can be calculated. The initial experiments were performed on the sodium salt of resorufin (Fig. 27) in



Resorufin

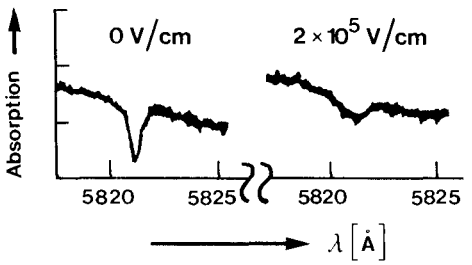


Fig. 27. Stark broadening of a photochemical hole of the sodium salt of resorufin in poly(methyl methacrylate) films [106].

poly(methyl methacrylate) films[106]. From these experiments one could infer a change of the dipole moment of 0.25 D upon excitation to the S_1-state. If holes are burned while an external field is applied[107,108], the hole-spectrum can subsequently be scanned by scanning the external field (Fig. 28). The maximum hole depth is achieved if the field

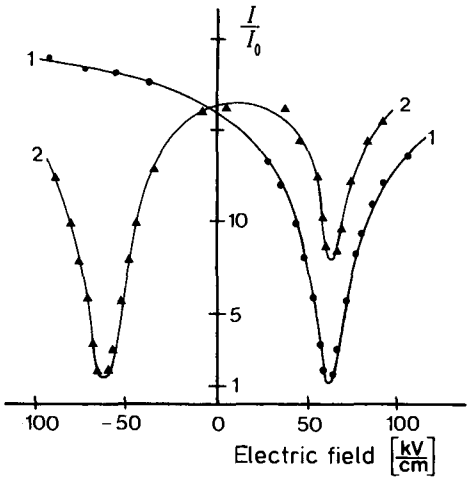


Fig. 28. Line shape of a photochemical hole as a function of the external electric field. System: Perylene in poly(vinylbutyral). 1) Hole burnt at a field of +60 kV/cm. 2) Additional hole burnt at a field of −60 kV/cm [107].

equals that at which the photochemical reaction was performed, in both magnitude *and* direction. The hole can therefore be viewed as a "memory" of the field strength and direction during the PHB photochemistry.

12. Non-Resonant Holes and Correlation Effects

Each photochemical hole burnt at the laser frequency ω_L must, in principle, appear in all other optical bands of the photoreactive molecule. A photochemical hole can therefore be investigated off-resonance at a frequency which is far removed from that of the laser. This experiment raises the question of what information can be gained using such a procedure.

Figure 29 gives an example of non-resonant hole burning: A hole was produced in the first vibrational band of 1,4-dihydroxyanthraquinone at ca. 5030 Å. As a consequence, a whole sequence of holes appears in the 00-band of the molecule. The non-resonant holes in the 00-band are considerably wider than the resonant hole at frequency ω_L. Figures 30 and 31 give a more detailed view of this situation. The occurrence of multiplets of holes was first observed by *Kharlamov* et al.[109]. Multiplets appear because the difference in the frequencies of vibrational states can be smaller than the inhomogeneous band width. Hence, irradiation at ω_L leads simultaneously to photochemical holes at various sites, which appear at different frequencies in the 00-band.

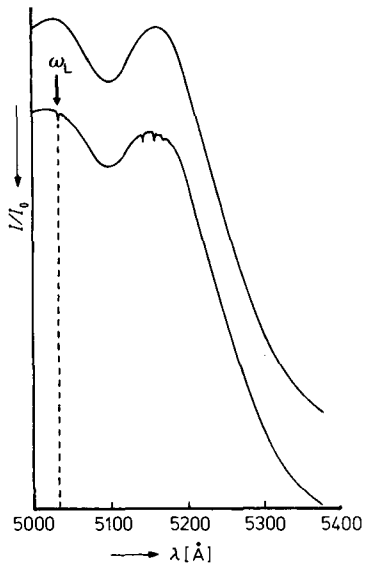


Fig. 29. Absorption spectrum of quinizarin in an ethanol-methanol glass (3 : 1) before and after hole burning at 5032 Å (1 mW/cm², T = 1.8 K). Several satellite holes appear in the 00-band of the spectrum [110].

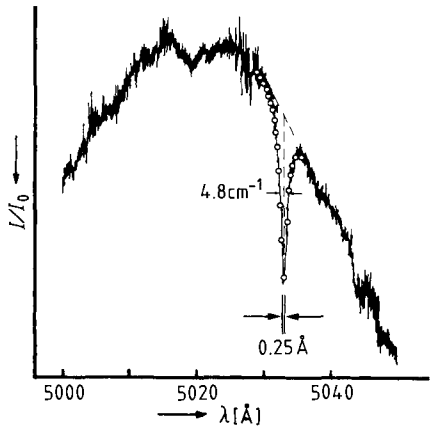


Fig. 30. Enlarged section of the spectrum of Figure 29. Resonant hole [110].

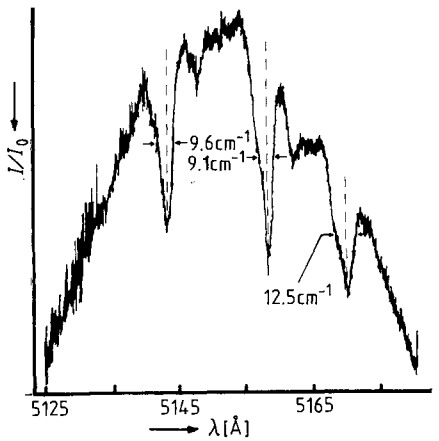


Fig. 31. Enlarged section of the spectrum of Figure 29. Nonresonant satellite holes [110].

If one wants to calculate the hole shape and hole width of the relaxed holes[110], a joint probability distribution must be considered. This distribution determines the probability of detecting a photochemical process at frequency ω_2 (of the inhomogeneous 00-envelope), initiated with laser irradiation into a vibronic transition at ω_1. This is rather analogous to the problem of correlating the errors in two variables[111]. In the simplest case, the distribution function is given by a two-dimensional Gaussian distribution [eq. (47)].

$$G(\omega_1-\omega_n,\omega_2-\omega_0)=\frac{4\ln 2}{\pi\Gamma_0\Gamma_n\sqrt{1-\rho^2}}\exp\left\{-\frac{4\ln 2\cdot(\omega_1-\omega_n)^2}{\Gamma_n^2}\right\}\exp\left\{-\frac{4\ln 2\cdot[(\omega_2-\omega_0)-(\omega_1-\omega_n)\hat{S}]^2}{\Gamma_0^2(1-\rho^2)}\right\} \quad (47)$$

$\hat{S}$ is a scaling factor, which becomes 1 if the inhomogeneous widths Γ_n of the state n (here a vibrational state) and Γ_0 of the state 0 are identical. ρ Characterizes the degree of correlation:

$$\rho\equiv\frac{\langle(\omega_1-\omega_n)(\omega_2-\omega_0)\rangle}{\Gamma_n\Gamma_0};\qquad 0\le|\rho|\le 1 \quad (48)$$

By examining two limiting cases, the significance of ρ becomes apparent. If $\rho=1$ complete correlation results; the second Gaussian function in equation (47) ist a δ-function and there is complete site selectivity in the non-resonant state. The widths of the non-resonant holes in this case are narrow and determined by the pertinent dephasing times. (The fluorescence from the non-resonant state is also narrow.) If the condition $\rho=0$ holds, the second Gaussian function in equation (47) has a width of Γ_0, i.e. a state which had been site-selected in the vibrational level n will be spread over the complete inhomogeneous band characterizing the 00-transition. In the latter case no narrow holes appear at the origin. In reality, one finds the situation of intermediate correlation. Here the hole shape can be calculated by a convolution of the zero-phonon lines $z_n(\omega)$ and $z_0(\omega)$ with the corresponding inhomogeneous profiles given above can be measured. If instead of focussing on a (i.e. to a convolution of a Gaussian and Lorentzian profile). If the homogeneous line widths in the states n and 0 are small compared to the width of the non-resonant holes, the shape of the non-resonant holes is Gaussian and their widths are given by $\Gamma_0(1-\rho^2)^{1/2}$.

By measuring this width (Figs. 30 and 31), one can calculate the loss of correlation between the vibrational state considered and the electronic origin: for quinizarin, $1-\rho\approx 10^{-5}$.

This means that the vibronic transitions are highly correlated with their electronic origin. It is only because of the narrow hole width that correlation losses as small as those given above can be measured. If, instead of focussing on a vibrational state n, one focussed on a different electronic state, for amorphous hosts, a vanishing correlation occurs as a rule. However, there is a possibility in crystalline materials that a certain degree of correlation may still exist even for different electronic states. Experiments probing the degree of correlation can therefore be looked upon as experiments which shed light on the role played by the solvent in optical excitation processes.

To understand the correlation phenomena discussed here, one has to consider a microscopic model. *Gorokhovskii* and *Kikas*[112] assumed that the inhomogeneity not only affects the various electronic levels, but also independently the vibrational levels. Figure 32 reflects this argument for an energy level scheme. If one excites into a vibrational level, two different sites are excited which have slightly different vibrational energies, but which, nevertheless, absorb at the same frequency ω_L. In the 00-transition both sites differ in frequency by the difference of their vibrational energies. If instead of two sites one has a complete site distribution, the above argument leads to an inhomogeneous broadening of the vibrational frequencies. This broadening is, on a relative scale, comparable to the inhomogeneous broadening of electronic levels. Besides correlation effects, using non-resonant holes, one can study the vibrational frequencies of photoactive molecules in the excited state[109,113]. Even in glasses, these frequencies can be studied with great accuracy. These experiments complement FLN techniques which allow the determination of ground state frequencies. By using both PHB- and FLN techniques vibrational frequency changes upon electronic excitation of molecular states can therefore be measured with great accuracy.

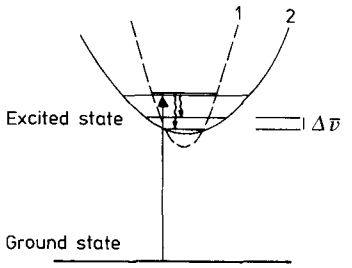


Fig. 32. Microscopic model describing the observed vibrational inhomogeneities. Sites 1) and 2) have slightly different vibrational energies.

13. Amorphous Solids

In 1976 the first fluorescence line narrowing (FLN) experiments were performed using inorganic glasses doped with paramagnetic ions and it was observed that optical properties in crystalline systems were quite different from those in amorphous solids[114]. For example, the homogeneous line width did not increase with T^7 (see Section 10), but increased with a lower temperature exponent. Similar observations were made for ESR and NMR experiments[115-117]. In addition, the observation was made that the homogeneous line width in glasses was much larger than that in crystals[114,118,119].

At first, these results came as a surprise, because it was known that the Debye model could be applied to glasses, and that optical line widths were mainly determined by elastic phonon scattering. A comparison of these new findings with results obtained from experiments on organic glasses created some new aspects. FLN experiments could only partly be evaluated due to the above discussed difficulties concerning correlation effects. Most new aspects therefore came from hole burning experiments[11,45,46,61,106,119] (see also [5]). Even the initial experiments indicated that the optical line widths in organic glasses were larger than those typical of inorganic glasses[46]. The measured hole widths were, even at 2 K, almost a wavenumber; this was an important fact, which had to be taken into account by theoretical considerations. As we have seen in Section 3, the homogeneous line width as $T\rightarrow 0$ is given by the "Heisenberg-limit", i.e. by the lifetime

of the excited state [eq. (10)]. Hole burning experiments, however, showed deviations from the Heisenberg-limit of up to three orders of magnitude, and there was considerable discussion as to the possibility of a residual line width as $T \rightarrow 0$. This discussion was interesting, because some systems, like porphin, allowed an extrapolation to the "Heisenberg-limit" as $T \rightarrow 0$[120-122] (with a power law $T^{1.33}$). Similar results were obtained for chlorin in polymer films[123]. The various conflicting data showing different temperature exponents and different residual line widths stimulated various theoretical model calculations[44,46,119,124,125-129]. One of the salient points of most models was a coupling mechanism of the dye probe molecules to the double-well potentials of the glassy state (Fig. 33a). If coupling to a single double well potential is considered, one has to deal with a total of four levels (Fig. 33b). It is of importance that a glass is, by definition, a system which is not in thermodynamic equilibrium; it has a residual entropy at $T=0$. Therefore, even at this temperature relaxation processes can occur via phonon emission (Fig. 33b), and can contribute to the line width. For a final assessment of this situation, however, a complete knowledge of the microscopic glass parameters would be necessary: Such parameters are barrier heights and energy values of the TLS levels, coupling matrix elements, veclocities of sound, etc. With these parameters still undetermined, the question as to the "true" homogeneous line width has no definite answer, yet.

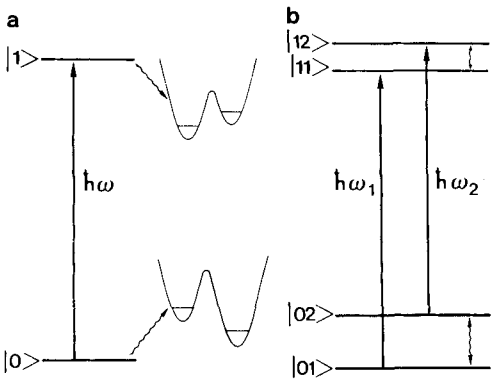


Fig. 33. a) Model describing the coupling of an optical transition to the tunneling potentials of a glass. b) Generalized level scheme. The symbols $|0\rangle$ and $|1\rangle$ correspond to the electronic excitations. The symbols $|01\rangle$, $|02\rangle$ and $|11\rangle$, $|12\rangle$ symbolize the corresponding tunneling states in the ground and excited states, respectively.

New theoretical aspects were introduced by considering "fractal dimensions"[130]. We can visualize this new concept by constructing a glass through areas of solid material, which are statistically interrupted by areas of "free volume". The general topological properties of such a composite system can, in general, not always be described by a three-dimensional model. The topology could, for example, be mainly two-dimensional with some "local defects" pointing into the third dimension. This is important for calculations of the phonon density of states, which can be different from the usual situation encountered in a three-dimensional lattice. The new dimensionality is smaller than three, yet, larger than two: One can speak of "fractal dimensions", whose elementary excitations are termed "fractons". If the TLS-levels are coupled to fractons, instead of to phonons, one can expect different power laws for the optical line width due to the different density of states[131]. Under certain conditions (percolating network, dipole-quadrupole coupling) one arrives at a power law of $T^{1.33}$. There is, however, a limitation to the applicability of fracton excitations. The theory can only be applied above a critical temperature T_c. At the critical temperature the average phonon wavelength is of the length of a structural domain. Therefore, one has to consider domain excitations for $T > T_c$ and thermal phonon excitations for $T < T_c$. In the latter case the domain structure is of little relevance and a simple Debye spectrum can be assumed. A temperature law of $T^{1.33}$ has also been obtained by other theoretical approaches[129,134].

The concept of two-level systems also leads to further, interesting consequences (Fig. 33b): Since the TLS-splitting is, in general, different in the ground and excited states, the transitions 1 and 2 of the four-level scheme are non-degenerate. At low temperatures this difference in TLS-splittings contributes to the optical line width. It can be assumed that, at high temperatures, the relaxation pathways shown in Figure 33b are so efficient that optical "exchange narrowing" takes place. If one were to assume that the relaxation processes slow down at low temperatures, an increase of the line width with decreasing temperature would be expected, as is shown in Figure 34[132]. Line broadening of this type with decreasing temperature is well known in NMR spectroscopy; however, to our knowledge no comparable results have been obtained in the optical domain, other than the preliminary data on amorphous polymers.

The discovery of irreversible contributions to the optical line width of dye molecules in glasses is of considerable importance[45,65]. Similar phenomena are not known from single crystal data and, hence, have to be discussed in some detail.

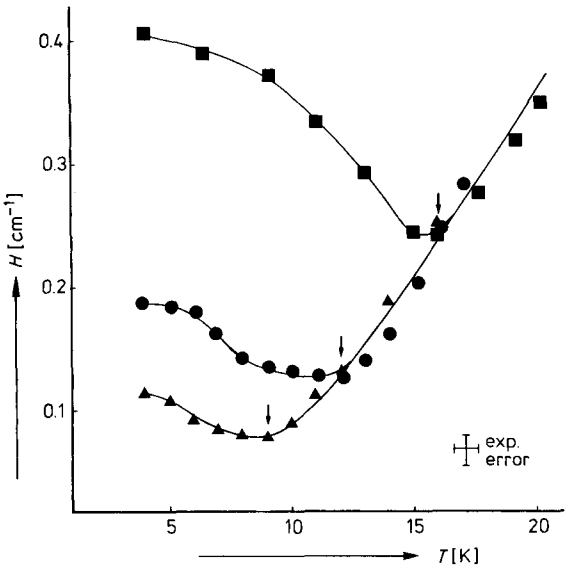


Fig. 34. Hole width as a function of temperature for phthalocyanine in polyethylene. The arrows mark the burning temperature. The increase of line width with falling temperature is rather unusual [132].

We start with the concept that a glass can be described by a distribution of double well potentials. In this model a "particle" can tunnel from the left potential minimum to the right potential minimum: in thermal equilibrium both processes occur. Associated with the tunneling processes are changes in the optical energy of the particles, since the potential curves are different in the ground and excited states (Fig. 33a). It is evident that the tunneling dynamics do not change the total number of molecules absorbing at a given frequency and, hence, the inhomogeneous line profile does not change in time and temperature; in other words the "site population" is in a stationary state.

This situation changes if, by light irradiation, a hole is burnt into the inhomogeneous distribution. The equilibrium is then perturbed and more particles tunnel into the hole relative to those tunneling out of it. This process leads to a change in line width by spectral diffusion[124, 133, 134]. Processes of this kind are always present and can be detected with high sensitivity in hole burning experiments at low temperatures (5 K in Fig. 35a) and by subsequently cycling the temperature. At higher temperatures the rates determining spectral diffusion increase via thermally assisted processes. The glassy state moves towards a state of new quasi-equilibrium. If the temperature is recycled to the low value again, the new state is frozen in and can be evaluated spectroscopically. In the case of quinizarin, the increase in line width is a factor of two. The hole width changes irreversibly with temperature; it becomes dependent on the sample history, a characteristic feature of non-equilibrium systems.

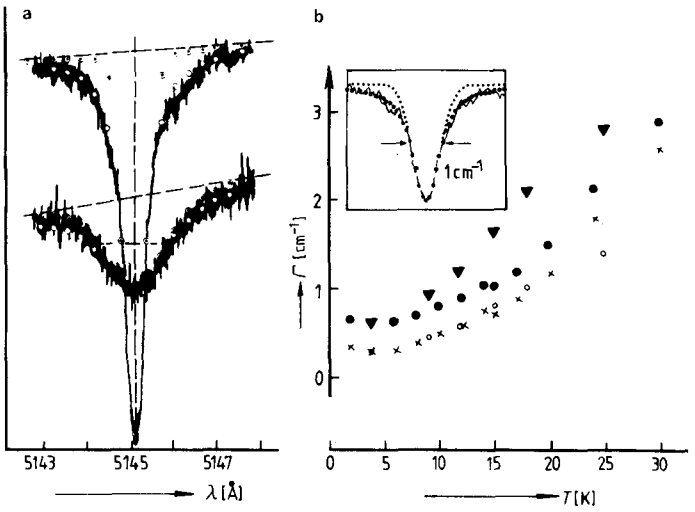


Fig. 35. a) Irreversible contributions to the line width. Both holes were burnt at ca. 5 K. The broad hole was subsequently exposed to a temperature cycle during which the sample was rapidly warmed up to 20 K. System: Quinizarin in ethanol glass [45]. b) Hole width as a function of temperature. ▲: Burning temperature equals temperature of spectroscopic experiment. ●: Burning temperature 2 K. ○, ×: Reduction of both curves to one master curve (good fit up to 20 K) [65]. System: Quinizarin in boric acid [45].

Because of these irreversible diffusion processes, one has to proceed with extreme care if it is desired to measure a homogeneous line width and its temperature dependence. If, for example, a hole is burned at low temperatures and one subsequently investigates the hole at higher temperatures, the result obtained differs from that had the hole burning process been performed at each individual temperature point (Fig. 35b)[45, 65].

At present, the time scale of these diffusion processes is not known exactly. It seems that there are processes which occur on the T_1-time scale, but there are also very slow processes. The different time scales arise because of the different barrier heights and the different tunneling distances and masses.

Hole burning offers a means of investigating the time scale of such diffusion processes. It should be mentioned, however, that spectral diffusion in photochemical hole burning can be due to two different processes: It can be caused from the reorientation of molecules in the ground-state (physical dark process) and can also be caused by a back reaction from the $|P\rangle$ state to the $|R\rangle$ state (Fig. 13) (chemical dark reaction). Both processes may change the hole width in a different way.

The chemical dark reaction has been investigated in only a few systems[135, 136]. It was found for quinizarin in alcohol glasses that the reaction occurs on a logarithmic time scale (Fig. 36)[136]. Between 1.3 and 4.2 K the slopes of the logarithmic decay curves show little temperature dependence, but exhibit a pronounced isotope effect upon deuteration of the sample. We would like to discuss briefly how such a behavior can be understood.

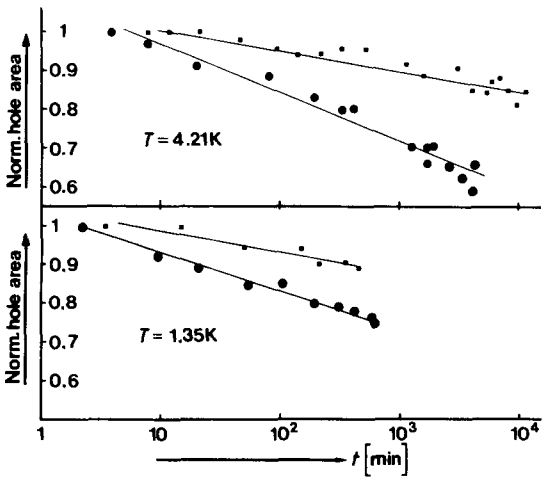


Fig. 36. Hole recovery as a function of time using the system quinizarin in ethanol-methanol glass (3 : 1) ● and in perdeuterated ethanol-methanol glass (3 : 1) ■. The slopes show a pronounced isotope effect [136].

Two main points have to be considered: a) The back reaction occurs via tunneling and b) the distribution of the reaction rates is given by the corresponding tunneling rates, as determined, for example, by measurements of the specific heat. Point a) is corroborated by the experimentally determined isotope effect. Point b) is plausible, since the back reaction, which involves reorientation of a hydrogen bond, is matrix controlled, i.e. depends on the local geometry of the solvent cage. If one accepts these assumptions, the number of molecules which have returned to the educt state after a time t can be calculated by integrating the rate distribution function:

$$\frac{n}{n_1} = N_0 \int_R^{R_1} p(R)\,\mathrm{d}R \qquad (49)$$

where n_1 is the number of molecules in the photoproduct state after a time t_1 has elapsed between hole burning and the first probing experiment. $p(R)$ is the distribution function of relaxation rates, as obtained from specific heat measurements[34-36]:

$$p(R) = \frac{\hat{P}}{2} \cdot \frac{1}{R\sqrt{1-R/R_{max}}} \tag{50}$$

where R_{max} is the fastest relaxation rate, R_{min} is the slowest rate, and $\hat{P}$ is a constant. The constant N_0 normalizes the number of particles. It is clear that for different observation times different relaxation rates $R = 1/t$ are observed. The fastest rate which can be observed in a hole burning experiment is given by $R_1 = 1/t_1$. If it is assumed that $1/t_1$ arises because of the slow time scale of our experiment, i.e. is small compared to R_{max}, then the square root in equation (50) can be neglected. After integrating equation (49), one obtains an expression for the relative hole area which shows a logarithmic time dependence

$$\frac{A}{A_1} = 1 - \left[\ln \frac{R_1}{R_{min}}\right]^{-1} \ln \frac{t}{t_1} \tag{51}$$

From the slope of the hole decay, as given in equation (51), the ratio of the rate constants R_1/R_{min} can be estimated. The ratios vary, for the various experiments, over a vast range, i.e. 8 orders of magnitude for protonated alcohol glass and 19 orders of magnitude for deuterated alcohol glass[136]. A logarithmic decay law corresponds to the slowest possible decay kinetics. The holes therefore persist over very long time intervals.

Finally, the problem of the large optical line width of holes has to be addressed. A typical example is quinizarin, whose hole width in an EtOH/MeOH glass at 1.3 K is 0.55 cm^{-1}. Power- and saturation-broadening can be ruled out. This value is two to three orders of magnitude removed from the "Heisenberg-limit" which should be valid as $T \rightarrow 0$. The question therefore arises as to whether or not this line width can be considered as the homogeneous width. Alternatively the following situation could be conceived: It is feasible that fast spectral diffusion processes set in immediately after the hole burning has created a non-equilibrium situation. This spectral diffusion could, in principle, also mask photochemical saturation (i.e. refilling of a hole which is close to the bottom of the band).

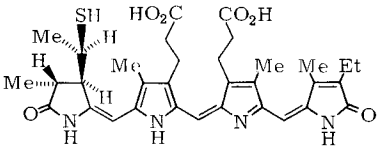
Spectral diffusion can also be initiated by external parameters[42, 137-140]. An ultrasonic pulse, for example, can be partly absorbed by the TLS-levels and, thus, lead to changes in the optical energy levels. Consequently, a spectral hole can be refilled by sound waves. In this respect one can look upon a hole as a "phonon memory"[42].

For a more detailed view of the optical properties of glasses it must finally be considered that not only the TLS-parameters are given by distribution functions, but also most other parameters which enter the model description (Section 9); for example, the Debye-Waller factor, the photochemical yield, and the thermal stability of the photoproduct[64]. Even the homogeneous line width need not be uniform[5]. All these parameters contribute to the spectral properties and to the time dependencies which characterize hole burning. It can therefore be appreciated that optical hole burning can be used as a sensitive tool for investigating subtle aspects of the physics of the amorphous state.

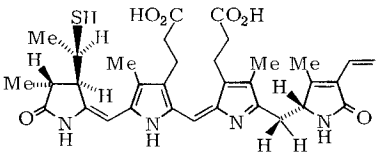
14. Photochemical Hole Burning in Biological Systems: Phycobiliproteins

14.1. Antenna Pigments

Chlorophyll is the most essential part of the photosynthetic reaction center, but has a comparatively low absorption coefficient in the visible spectrum. In photosynthetic organisms a great deal of the sunlight is absorbed by so-called antenna pigments. These channel the absorbed photon energy to the reaction centers. The phycobiliproteins such as phycoerythrin (PE), phycocyanin (PC), and allophycocyanin (APC) (see Fig. 37) characterize a class of antenna pigments. The pigments contain several dye molecules (chromophores) which are coupled via energy transfer processes (see e.g. [11]). The chromophores are covalently bound, at least at one position, to their protein environment and their excitation energy differs both due to the different micro-environment of the protein and their different structures. The energy transfer process between the chromophores is therefore non-resonant.



Phycocyanobilin



Phycoerythrobilin

Conventional optical spectroscopy of antenna pigments is handicapped by low optical resolution due to the large inhomogeneous band width of the pigment spectra. Until

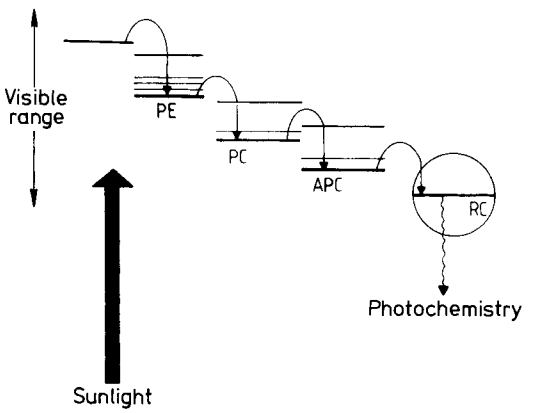


Fig. 37. Energy levels and energy transfer in the antenna pigments. PE: phycoerythrin, PC: phycocyanin, APC: allophycocyanin, RC: reaction center.

now it was therefore impossible to investigate the spectroscopy of the various chromophores selectively. Hole burning is a new approach in this direction, because it increases the optical resolution by several orders of magnitude. The first experiments on isolated antenna pigments were published in 1981[141]. In the following section we summarize the results.

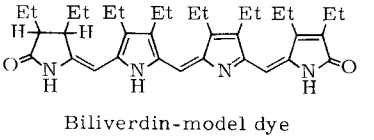
14.2. Low Temperature Photochemistry of Antenna Pigments

Figure 38 shows a sequence of photochemical holes which have been burnt into the visible bands of phycocyanin (6270 Å) and allophycocyanin (6250 Å). The numbers label the sequence of hole burning experiments. The data indicate that the creation of a low energy hole has no influence on a hole previously burned at higher frequency; however, hole burning at high frequencies seems to partly refill holes previously burned at lower frequencies. The creation of hole 3, for example, refills hole 2, but does not affect hole 1.

Fig. 38. Photochemical holes in the lowest energy band of phycocyanin + allophycocyanin. The numbers label the sequence of hole burning events [141]. $T = 1.8$ K, resolution 0.15 Å.

From this it can be concluded that the hole burning process is photo-reversible and that the photoproduct absorbs at energies higher than the absorption energies of the educt. It appears that the photoproduct state cannot be reached directly from the excited educt state (S_1). Most probably it is reached through an intramolecular relaxation process, i.e. intersystem crossing (ISC) to the triplet state T_0. In the latter case the inverse fluorescence lifetime would be an upper bound for the photochemical reaction rate.

We believe that the case considered here is a light-induced proton transfer. This assumption is supported by experiments using a model chromophore. Figure 39 shows an absorption spectrum of a biliverdin dye in an alcohol glass matrix. The spectrum splits into two bands at low temperatures. It is believed that the high energy band is due to the neutral dye molecule and that the low energy band is associated with the protonated species[142]. Only the protonated form, however, exhibits PHB-photochemistry. In general, photochemical hole burning is not possible in all spectral ranges. For example, for phycocyanin within the visible spectral range of absorption, the low energy band shows efficient hole burning, whereas the high energy band exhibits no measurable photochemical yield. Possibly the corresponding chromophore is deprotonated similarly to the model dye.



Biliverdin-model dye

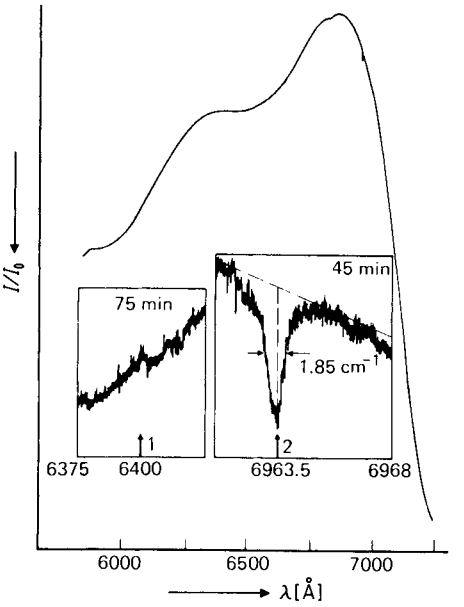


Fig. 39. Hole burning experiments using a biliverdin model dye. Only the protonated species shows measurable photochemistry (see arrow) [141]. Matrix: Ethanol-methanol glass (3:1), $T = 1.8$ K, resolution 0.15 Å.

14.3. Energy Transfer and Satellite Holes

Phycoerythrin behaves similarly to phycocyanin, the main difference being that hole burning occurs in both the high and low energy bands (Fig. 40). It is interesting to note that the creation of one hole at high energies leads to a whole series of holes which are displaced by ca. 600 cm^{-1} to lower energies. At first, one could attribute this phenomenon to vibronic hole burning, as described in Section 12. There are, however, several arguments which can be raised against such an interpretation, the principal one being that no vibrational transitions can be observed in the fluorescence spectrum. It is therefore more likely that the satellite holes are due to energy transfer between the various chromophores of the protein. In this case, one can distinguish three limiting cases.

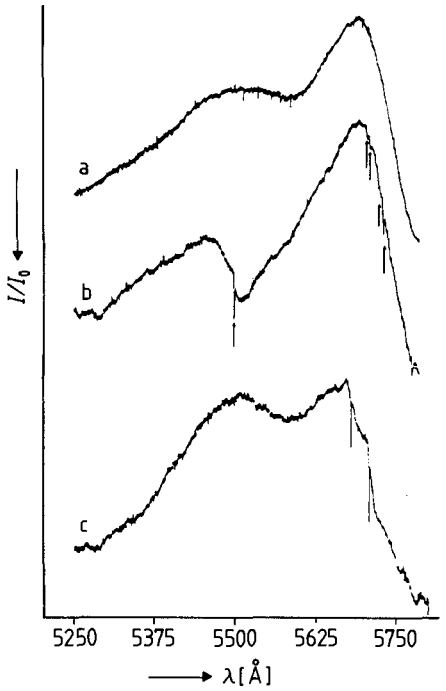


Fig. 40. Hole burning experiments using phycoerythrin [141]. a) Spectrum prior to irradiation. b) Spectrum after irradiation at 5500 Å (1 mW/cm², 10 min). The spectrum shows off-resonant satellite holes (arrows). c) Photochemical hole burning in the low energy band. No satellites appear at higher energies. Matrix: Glycerol/buffer (3:1), $T = 1.8$ K, resolution 0.2 Å.

a) The "fast transfer limit", which is characterized by

$$k_{ET} \gg k_{PR}$$

where k_{ET} is the energy transfer rate and k_{PR} is the rate of the photoreaction. In the "fast transfer limit" the excitation energy is transferred to the energy acceptor before a photoreaction can occur. In this case, only the satellite holes would be observed.

b) The "slow transfer limit", which is characterized by

$$k_{ET} \ll k_{PR}$$

In this case only a resonant hole can be observed.

c) The "intermediate transfer limit", which is characterized by

$$k_{ET} \approx k_{PR}.$$

In the latter case a fraction of the molecules can undergo a photoreaction in the time required for energy transfer to the acceptor molecules. Therefore resonant, as well as off-resonant, holes can be observed.

The PHB experiments in phycoerythrin can, in principle, be explained using the "intermediate transfer limit". As we discussed previously, the fluorescence rate and the photoreaction rate at 2 K must be two competing processes; this assumption is corroborated by fluorescence measurements[143]. Within the framework of the above model it is of special relevance that the satellite holes are rather narrow. This implies a very good correlation between the energy levels of both donor and acceptor molecules ($1-\rho \approx 10^{-4}$). As a consequence, the local molecular environment of the chromophores must be similar, i.e. well correlated from one protein molecule to the other. This would support the concept of a highly structured protein unit with the dye molecules being surrounded by a reproducible local environment (aperiodic crystal). This unit would, to a large extent, shield the inhomogeneities of the solvent cage, at least for some of the chromophores. From these arguments one would also conclude that the energy transfer to the lowest energy chromophore is a relaxation process, which channels the energy downhill along a well defined "energy ladder". The results of polarization experiments seem to support such a view[143].

Based on the sharp structure of the zero-phonon holes, one might conclude that the fluorescence is also structured if observed under FLN conditions. This, however, has not been found for phycoerythrin and phycocyanin[144]. Obviously, there is no high degree of correlation between the absorbing and the fluorescening chromophores, which have, as a rule, the lowest energies. One might speculate that these chromophores lie close to the protein surface and are, therefore, exposed to the inhomogeneous environment of the glass matrix (glycerol/buffer solution).

15. Technical Applications

Photochemical hole burning has potentially interesting applications. Quite evident is the application for creating ultra-narrow optical filters with band widths in the MHz range. Holes could also be used as frequency markers (cf. Section 11) and for stabilizing lasers. It has been reported that holes can be used to modulate optical pulses[145, 146]. A rather attractive application has been pursued since 1978: The use of PHB for ultra-high density storage of data in the optical range[147–149]. Figure 41a shows a possible storage scheme. It consists of a spatial matrix of optical bits which can be scanned by a laser beam. If the laser hits a transmitting spot, it detects a logical 1 (an opaque spot would be 0). The highest storage density of such a scheme would be given by the minimal spot size of the laser focus,

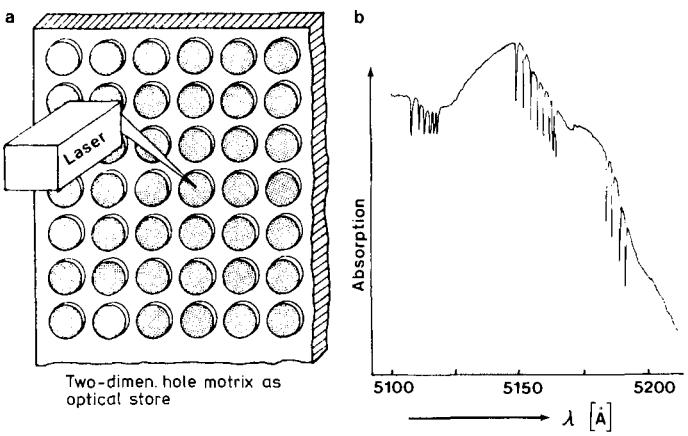


Fig. 41. a) Scheme of an optical store based on photochemical hole burning. b) Photochemical holes as bits (units of information) in the frequency domain. System: Quinizarin in ethanol-methanol glass (3:1, $T = 1.8$ K).

which is in the order of λ^2, where λ is the laser wavelength (diffraction limit). The highest possible storage density using light with the wavelength of 500 nm would therefore be 10^8 bits/cm^2. If the material used in Figure 41a is replaced by one which allows hole burning, one can conceive a frequency selective storage scheme and the bit density can be increased by a factor of 10^3 to 10^4. This factor is roughly given by the ratio of the inhomogeneous line width of the storage material divided by twice the homogeneous line width. Figure 41b shows a sequence of holes burnt into the lowest absorption band of quinizarin in an ethanol/methanol glass. The figure shows that the bits can be stored in a frequency selective fashion.

In PHB-storage the frequency is used as an additional storage dimension, i.e. a two-dimensional spatial store would be three-dimensional. One could even conceive a four-dimensional store by using spatially three-dimensional holograms[150–152]. With such a method one would approach the storage density of the human brain.

The technical problems for hole burning storage are formidable. The least of these is the refrigeration of the storage material to 4 K, whereas the major problems arise from limitations in the speed of reading and writing the information. These speeds are not solely limited by frequency addressing and spatial addressing; they are also limited by the photochemical reaction rate of the photoreactive material. Last but not least, signal to noise considerations have to be discussed in detail[153]. In the technical approach to the problem great success has been achieved using frequency modulation techniques[154, 155]. These methods show the feasibility of data rates in the MHz range. Simultaneous reading and writing in several "frequency channels" could possibly raise the data rates close to the GHz range.

The problems which still bottleneck the method stem from optimizing the photochemical system. It would be desirable to have an active material which operates in the wavelength range of semiconductor lasers (800–900 nm), which are cheap and can be easily tuned and modulated. In this wavelength range color centers in alkali halides have been used as active materials. These systems have the disadvantage of narrow inhomogeneous line widths and of a rather limited hole lifetime (several hours). As a result, the information density, as determined by the factor $\Gamma/2\gamma_h$, is considerably smaller than that of organic materials. Judging from these criteria, organic materials would, in principle, be preferable.

Another problem arises because frequent reading processes gradually bleach the material and, hence, destroy the information. A possible solution to this problem is to use more than one light quantum (two-photon photochemistry)[81, 156]. This is illustrated in the energy level scheme in Figure 42: The frequency selective absorption of the first photon creates an intermediate state $|1\rangle$, most probably the lowest singlet state S_1; it is considered to be photostable. The photoreactive state $|a\rangle$ is reached by absorption of a second photon (Fig. 42a). This can also be reached with a second photon after a relaxation process to a long-lived intermediate state $|2\rangle$ (Fig. 42b).

Depending on the energies $\hbar\omega_1$ and $\hbar\omega_2$, the storage scheme can be designed such that irradiation to level $|1\rangle$ does not destroy the photochemical information. The disadvantage of two-photon schemes is their low quantum yield. Similar schemes have been devised for holographic imaging techniques (two-photon, four-level scheme[156]).

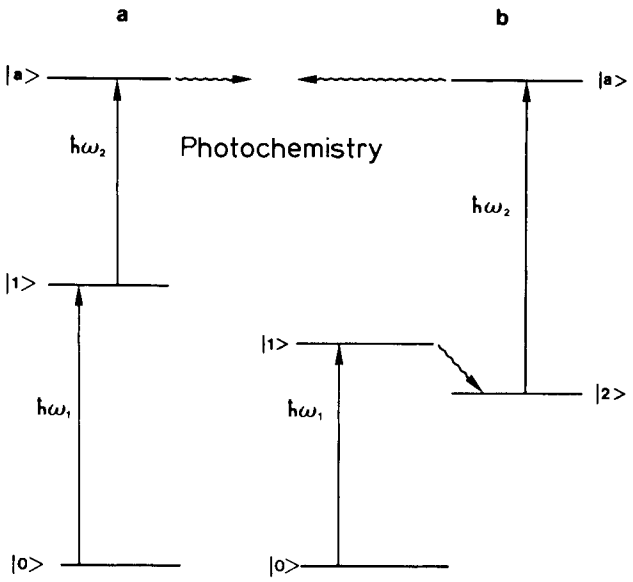


Fig. 42. Energy level scheme for hole burning via a two-photon process. a) Three-level diagram; b) four-level diagram.

From the point of view of the stability of the holes, the use of photochemical hole burning schemes appears safe. Even those photochemical holes which exhibit decay phenomena (see Section 13) decay on a logarithmic time scale, i.e. have the slowest possible relaxation mechanism.

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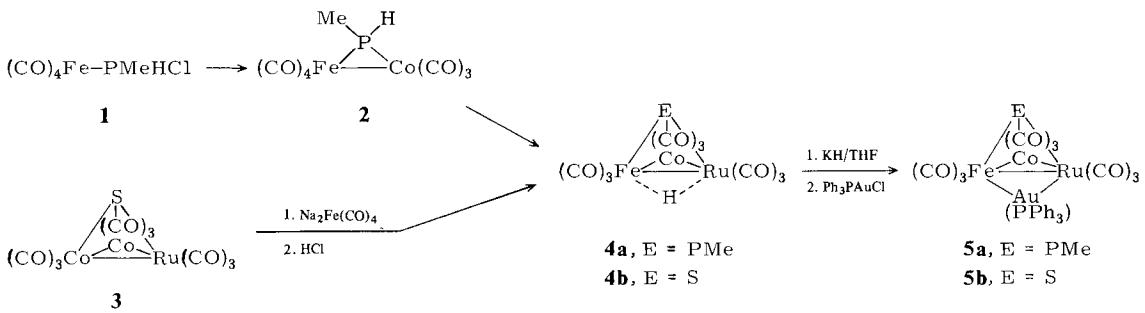
Stepwise Assembly of a Cluster with Four Different Metal Atoms**

By *Klaus Fischer, Manfred Müller,* and *Heinrich Vahrenkamp**

Heteronuclear organometallic clusters lend themselves more readily to systematic synthesis[1] and to mechanistic reactivity studies[2] than homonuclear compounds. Their chemistry still presents many challenges, and we have now met one of these: the stepwise synthesis of a cluster having four different metal atoms from four simple precursors.

The cluster **5a** is formed from the synthetic building blocks $MePCl_2$, $Fe_2(CO)_9$, $KCo(CO)_4$, $Ru_3(CO)_{12}$, and Ph_3PAuCl. We have previously described the reaction sequence reproduced in simplified form in Scheme 1 as far as compound **4a**[3]. Deprotonation of **4a** with KH and subsequent treatment with Ph_3PAuCl led to black **5a**[4]. An alternative route to the cluster type **5**, involving a metal exchange reaction[2,5], has been found for the μ_3-sulfido complex **5b**: **4b** is formed from **3** (cf. Scheme 1) and can be converted into black-red **5b** (yield 37%) by analogy to **4a**[6].

The constitutions of **5a** and **5b** were confirmed by X-ray structure analysis. A simplified molecular structure of **5a** is shown in Figure 1. Because of disorder, in the completely analogous structure of **5b** only the heavy atom framework could be determined unequivocally[7]. Like the hydride ligand in **4a**, the Ph_3PAu moiety preferentially adopts an edge-bridging site, and hence the heteronuclear tetranuclear clusters **5** exhibit a "butterfly" arrangement of the metal atoms.



Scheme 1. Synthetic pathway to the clusters **5**.

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[**] This work was supported by the Fonds der Chemischen Industrie, by Heraeus, and by the Rechenzentrum der Universität Freiburg. We thank Dr. *K. Steinbach*, Universität Marburg, for the mass spectrum.

5a and **5b** are not the first clusters having four different metal atoms[8], and the reactions in Scheme 1 are also not novel. However, their combination to afford a multistep synthesis of **5a** and **5b** represents a further step in the sys-

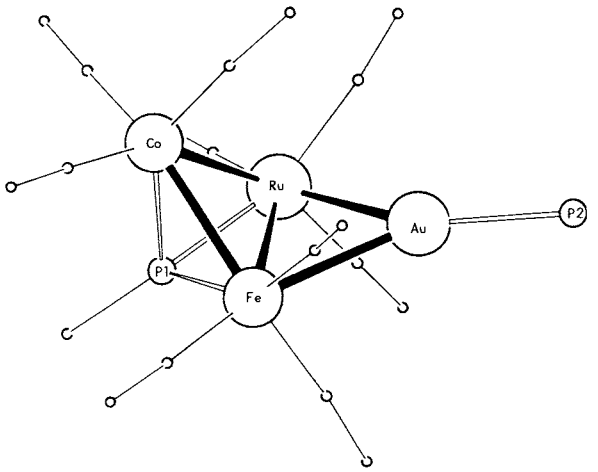

Fig. 1. Molecular structure of the cluster **5a** in the crystal (without the phenyl groups at P2; small circles represent the CO ligands and the methyl group at P1. Important atom distances: Au–Ru 2.729(2), Au–Fe 2.677(2), Ru–Fe 2.914(3), Co–Ru 2.679(3), Co–Fe 2.678(4), Au···Co 3.957(3) pm. Dihedral angle AuRuFe/CoRuFe 122.3(2)°.

tematic development of the chemistry of cluster compounds. That the syntheses can be generalized, which is supported by the bridging effect of the μ_3-E ligand, is clear. Also, the presence of the "catalysis metal" ruthenium as well as the chirality of **5a** and **5b** suggest that these compounds may be useful practically.

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CAS Registry numbers:
4a, 87150-87-6; **4b**, 88425-72-3; **5a**, 88425-73-4; **5b**, 88425-74-5; Ph_3PAuCl, 14243-64-2; Fe, 7439-89-6; Co, 7440-48-4; Au, 7440-57-5; Ru, 7440-18-8

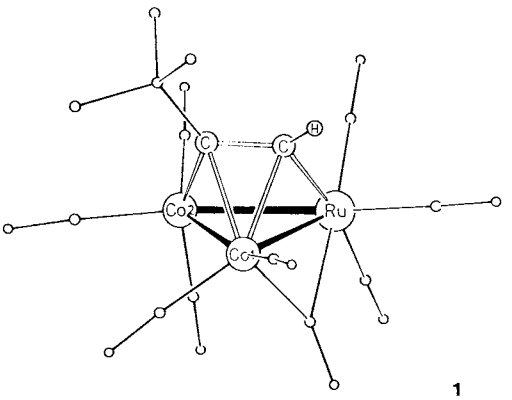
[1] W. L. Gladfelter, G. L. Geoffroy, *Adv. Organomet. Chem. 18* (1980) 207.
[2] H. Vahrenkamp, *Adv. Organomet. Chem. 22* (1983) 169.
[3] M. Müller, H. Vahrenkamp, *Chem. Ber. 116* (1983) 2311, 2322.
[4] Procedure: KH (18 mg, 0.45 mmol) is added to a stirred solution of **4a** (0.23 g, 0.45 mmol) in 20 mL tetrahydrofuran. After 15 min—the solution having changed from orange to dark red—Ph_3PAuCl (0.22 g, 0.45 mmol) is added. After stirring for an additional 15 min and removal of the solvent, the residue is extracted with 50 mL hexane. The filtrate is concentrated to 2 mL under reduced pressure, and the precipitate formed at −30°C recrystallized from 2 mL *n*-pentane: 35 mg black **5a** (8%), m.p. = 128°C, M_r = 973 (FD-MS).
[5] R. A. Epstein, H. W. Withers, G. L. Geoffroy, *Inorg. Chem. 18* (1979) 942.
[6] ^{1}H-NMR data ($CDCl_3$, int. TMS); **5a**: δ = 3.04 (Me, doublet, J = 13.6 Hz), 7.50 (Ph, multiplet); **5b**: δ = 7.20 (Ph, multiplet). IR data (C_6H_{12}, cm^{-1}); **5a**: 2066 w, 2037 vs, 2018 vs, 2001 m, 1994 sh, 1980 w, 1972 w, 1958 w, 1941 w; **5b**: 2082 s, 2050 s, 2038 vs, 2005 s, 1992 sh, 1980 w, 1947 w.
[7] **5a**: monoclinic, $P2_1/c$, a = 1296.2(4), b = 1508.2(5), c = 1726.4(4) pm, β = 105.07(2)°, Z = 4, 4242 reflections, R = 0.065; **5b**: triclinic, $P\bar{1}$, a = 1197.1(2), b = 1448.3(3), c = 922.8(2) pm, α = 93.45(2), β = 101.24(2), γ = 77.55(1)°, Z = 2, 3164 reflections R = 0.161. Further details of the crystal structure analysis can be obtained from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen, by quoting the depository number CSD 50581, the names of the authors, and the journal citation.
[8] F. Richter, H. Vahrenkamp, *Angew. Chem. 91* (1979) 566; *Angew. Chem. Int. Ed. Engl. 18* (1979) 531.

A "Cluster-Centered" Acetylene-Vinylidene Rearrangement**

By *Wolfgang Bernhardt* and *Heinrich Vahrenkamp**

The reactions of small hydrocarbon units on solid surfaces and model studies thereof on organometallic polynuclear complexes are of considerable practical significance. An example is the acetylene-vinylidene rearrangement HC≡CR → =C=CHR. Although numerous trimetal clusters with μ_3-alkyne[1] and some with μ_3-alkenylidene ligands[2] are known, corresponding conversions could previously only be postulated[2,3]. We have now succeeded, for one and the same carbonyltrimetal moiety, in isolating and characterizing the μ_3-η^2-alkyne complex and fully characterizing its rearrangement product, the μ_3-η^2-alkenylidene complex.

The 3,3-dimethyl-1-butyne-$RuCo_2$ complex **1** is formed at 5—15°C in 3—4 h *via* a "capping reaction"[4] between $RuCo_2(CO)_{11}$ and the alkyne in *n*-pentane (yield >90% after chromatography on silica gel). If **1** is heated for several hours in hexane at 60°C, it rearranges to the 3,3-dimethyl-1-butenylidene-$RuCo_2$ complex **2** in 81% yield. The constitutions of **1** and **2**, confirmed from their spectra[5],



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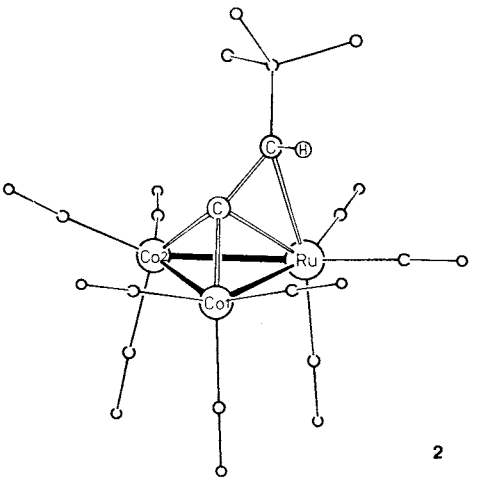

2

Fig. 1. Schematic molecular structures of the organometallic clusters **1** and **2** (small circles represent C and O atoms). Most important bond lengths in **1**: Co1–Co2 245.9(2), Ru–Co1 259.1(2), Ru–Co2 269.9(1), C–C 134(1) pm; in **2**: Co1–Co2 248.9(1), Ru–Co1 261.8(1), Ru–Co2 262.8(1), C–C 137(1) pm.

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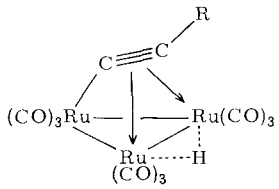
elemental analyses, and crystal structure determinations[6], prove indirectly that the previously described rearrangements of $RuCo_2$ complexes with acetylene ligands[3] lead to isomers with vinylidene ligands

$RuCo_2(CO)_9(\mu_3\text{-}\eta^2\text{-}HCC\mathit{t}Bu)$ **1** $RuCo_2(CO)_9(\mu_3\text{-}\eta^2\text{-}CCH\mathit{t}Bu)$ **2**

The atomic arrangements in **1** and **2** (Fig. 1) indicate the marked change in the bonding situation caused by the acetylene-vinylidene conversion. The CC multiple bond, which in **1** is parallel to the metal atom triangle, is inclined at ca. 47° to the triangular plane in **2**; and is *ca.* 3 pm longer in **2** than in **1**. The vinylidene ligand can therefore be considered as a M_3C-CHR carbenium ion stabilized by charge delocalization, as discussed previously for the isoelectronic $(CO)_9Co_3C-CHR$ cations[7].

Intermediates involved in the rearrangement of alkyne complexes into isomeric 1-alkenylidene complexes have not yet been observed, even for mono- and binuclear complexes. Initial migration of the acetylenic H atom to the metal to form an acetylide complex, which then tautomerizes to the vinylidene complex, appears plausible[8]. The geometrical relationship between **2** and the acetylide complex **3**[9] corroborates this. And also the ensuing step, the hydrogenation to the alkylmethylidyne complex, which e. g. is possible starting from $H_2Os_3(CO)_9(CCHR)$ to afford **4**[2], requires only slight steric changes. The alkyne-alkene-alkane conversion on a metal surface modeled by the sequence **1**, **3**, **2**, **4** is therefore consistent with a "straightening out" of the C_2 moiety above the metal atom plane.



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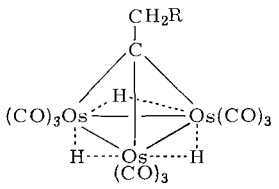

4

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German version: *Angew. Chem. 96* (1984) 139

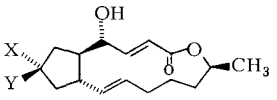
CAS Registry numbers:
1, 88495-88-8; **2**, 88495-89-0; $RuCo_2(CO)_{11}$, 78456-89-0; 3,3-dimethyl-1-butyne, 917-92-0

[1] E. Sappa, A. Tiripicchio, P. Braunstein, *Chem. Rev. 83* (1983) 203.
[2] A. J. Deeming in B. F. G. Johnson: *Transition Metal Clusters*, Wiley, New York 1980, p. 391; C. J. Cooksey, A. J. Deeming, I. P. Rothwell, *J. Chem. Soc. Dalton Trans. 1981*, 1718.
[3] E. Roland, H. Vahrenkamp, *J. Mol. Catal. 21* (1983) 233.
[4] E. Roland, H. Vahrenkamp, *Organometallics 2* (1983) 1048.
[5] ^{1}H-NMR data ($CDCl_3$, int. TMS) of **1**: $\delta = 1.19$ (9H), 8.17 (0.5H), 9.00 (0.5H); **2**: $\delta = 1.15$ (9H), 5.80 (1H). IR-data (C_6H_{12}, cm^{-1}) of **1**: 2095 w, 2056 vs, 2040 vs, 2030 vs, 2018 w, 2005 w, 1899 w; **2**: 2096 w, 2054 vs, 2045 vs, 2031 vs, 2014 m, 2008 sh. The two broad ^{1}H-NMR signals of intensity 0.5 suggest a rapid interconversion between two isomers of **1**, whose C≡C bonds are orientated respectively along an Ru—Co bond. Only one of these isomers is observed in the crystalline state [6].
[6] **1**: triclinic, $P\bar{1}$, $a = 1013.6(2)$, $b = 1328.4(2)$, $c = 820.4(1)$ pm, $\alpha = 106.31(1)$, $\beta = 112.68(1)$, $\gamma = 76.17(1)°$, $Z = 2$, 2928 reflections, $R = 0.061$. **2**: monoclinic, $P2_1/c$, $a = 877.8(2)$, $b = 1299.1(1)$, $c = 1728.8(2)$ pm, $\beta = 95.77(1)°$, $Z = 4$, 2911 reflections, $R = 0.046$. Further details on the crystal structure determination can be obtained from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen, by quoting the depository number CSD 50592, the names of the authors, and the journal citation.
[7] R. T. Edidin, J. R. Norton, K. Mislow, *Organometallics 1* (1982) 561.
[8] J. Wolf, H. Werner, O. Serhadli, M. L. Ziegler, *Angew. Chem. 95* (1983) 428; *Angew. Chem. Int. Ed. Engl. 22* (1983) 414; J. Holton, M. F. Lappert, R. Pearce, P. I. W. Yarrow, *Chem. Rev. 83* (1983) 135.
[9] M. Catti, G. Gervasio, S. A. Mason, *J. Chem. Soc. Dalton Trans. 1977*, 2260.

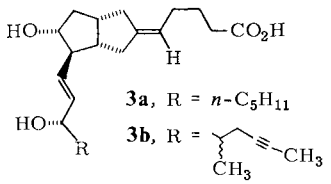
Enantioselective and Enantioconvergent Syntheses of Building Blocks for the Total Synthesis of Cyclopentanoid Natural Products**

By *Hans-Joachim Gais** and *Karl L. Lukas*

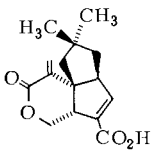
Because of their structures and biological properties, cyclopetanoid natural products and analogues such as brefeldin A **1**[1a], 7-*epi*-brefeldin A **2**[1b], and the 6a-carbaprostacyclins **3a**[1d] and **3b**[1e], and the pentalenolactone E **4**[1c], are rewarding synthetic targets. **1**, **2**[2a], and **3a** and **3b**[2b] have been prepared enantioselectively by total synthesis from the cyclopentenolactone **5**; **4** has not yet been completely synthesized from *ent*-**5**[2c]. We report here two novel efficient routes to **5** and *ent*-**5**, starting from *meso*-tetrahydrophthalic anhydride.



1, X = OH, Y = H
2, Y = OH, X = H



3a, R = n-C_5H_{11}
3b, R =



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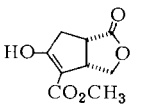

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Enantioselective saponification of the *meso*-diester **6** with commercial pig liver esterase (PLE) results in practically exclusive attack at the (1*R*)-ester group to afford the enantiomerically pure (1*S*,2*R*)-monoester **7** [99%, ≥99% *ee*, m.p. = 28°C, $[\alpha]_{365}^{20}$ +26.1 (0.89, H_2O)], the reaction proceeding on the mol scale (Scheme 1)[2c, 3a, b]. For the synthesis of 1 mol **7**, ca. 9000 U (90 mg) PLE, 1000 mL phosphate buffer (pH 7.0), 500 mL 2N NaOH, and a reaction time of 4 d at 25°C are required. Enantiomer resolution of *rac*-**7** with ephedrine or dehydroabietylamine enables large amounts of **7** *and ent*-**7** [m.p. = 28°C, $[\alpha]_{365}^{20}$ −25.9 (0.90, H_2O)] to be obtained enantiomerically pure (92%, ≥99% *ee*). The enantiomeric excess (*ee*) of **7** and *ent*-**7** was determined from the diastereomeric excess (*de*) of the ephedrine salts, which in turn was determined by ^{1}H-NMR spectroscopy from the different signals of the ester groups. Within the detection limits (≥1%), admixture of the respective other diastereomer did not occur. The absolute configuration of **7** and *ent*-**7** was established by X-ray structure analysis of the (−)-(1*R*,2*S*)-ephedrine salt of *ent*-**7** [m.p. = 158°C, $[\alpha]_D^{20}$ −35.9 (2.00, MeOH)]. The "pseudosymmetric" structure of **7** and *ent*-**7** permits both their conversion into the lactones **8** [$[\alpha]_D^{20}$ −85.4 (2.63, acetone)] or *ent*-**8** [$[\alpha]_D^{20}$ +85.2 (2.64, acetone)] (enantioconvergence[4]), respectively, and the synthesis of **8** and *ent*-**8**

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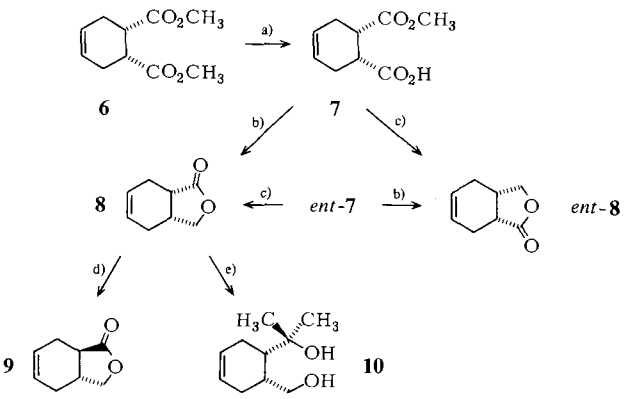
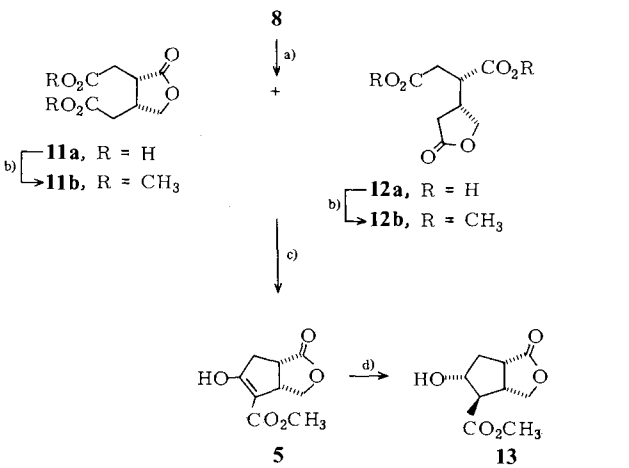
from **7** by optional chemoselective reduction of the ester or carboxy group to the hydroxymethyl group and subsequent lactonization (Scheme 1). For the ester group this proceeds by reduction with sodium and ethanol in liquid ammonia (**7**→*ent*-**8**, 82%) or with $LiBH(Et)_3$ (**7**→*ent*-**8**, 79%) and for the carboxy group via acid chloride and reduction with $NaBH_4$ in ethanol (**7**→**8**, 76%)[5]. Undesired



Scheme 1. a) PLE. b) $(COCl)_2$, $CHCl_3$, 25°C; $NaBH_4$, EtOH, −40°C; TsOH, PhMe, 110°C. c) Na, EtOH, NH_3, −78°C; NH_4Cl; conc. HCl. d) NaOH, H_2O, 100°C, 48 h; conc. HCl. e) MeLi, Et_2O, tetrahydrofuran, −78°C.

epimerization to afford the *trans*-lactones *ent*-**9** and **9**, respectively, in the conversion of **7** into **8** and *ent*-**8**, respectively, can be avoided within the limits of detection (≥1%). For comparison, epimerization of **8** on the preparative scale afforded **9** [m.p. = 98°C, $[\alpha]_D^{20}$ −155.0 (1.90, acetone)] [*ent*-**9**: m.p. = 98°C, $[\alpha]_D^{20}$ +155.1 (1.91, acetone)], whose reduction to the known (1*R*,2*R*)-4-cyclohexene-1,2-dimethanol [m.p. = 54°C, $[\alpha]_D^{20}$ −69.8 (2.97, $CHCl_3$)] allowed determination of the absolute configuration of **8** by a chemical correlation[2c,6] (Scheme 1). The *ee*-values of **8** and *ent*-**8** were determined indirectly on the dimethyldiols **10** [m.p. = 90—91°C, $[\alpha]_D^{20}$ +77.0 (1.68, CH_2Cl_2)] and *ent*-**10** [m.p. = 90—91°C, $[\alpha]_D^{20}$ −76.8 (1.63, CH_2Cl_2)] by ^{1}H-NMR spectroscopy (300 MHz) in the presence of the chiral shift reagent Eu(tfc)$_3$ from the methyl signals to ≥99% [*rac*-**10** + 0.6 equiv. Eu(tfc)$_3$ in $CDCl_3$ exhibits a $\Delta\Delta\delta = 0.12$ ppm][2c,6]. Within the limits of detection (≥0.5%), no admixture of the other isomer was detectable.

Oxidative ring cleavage of **8** leads to the dicarboxylic acids **11a** and **12a** (87%), whose esterification affords a 1:1-mixture of the isomeric lactone diesters **11b** and **12b** (91%). As expected[2c], both the pure diesters and the mixture can be converted regioselectively with KO*t*Bu into the cyclopentenolactone **5** (82%) [m.p. = 120—121°C, $[\alpha]_D^{20} = +190.0$ (2.48, CH_2Cl_2); *ent*-**5**: m.p. = 120—121°C, $[\alpha]_D^{20} = -189.3$ (2.46, CH_2Cl_2)], which exists almost exclusively in the enol form. The structure of **5** is proved by 400 MHz ^{1}H-NMR spectroscopy. A further structural proof was provided by an X-ray structure analysis of the hydroxy ester **13** [m.p. = 98—100°C, $[\alpha]_D^{20}$ +49.3 (1.13, ethyl acetate)] (Scheme 2). Using the strategy we have described here, **5** and *ent*-**5** are accessible rationally and enantiomerically pure by *enantioselective* (7 steps, 50% and 6 steps, 53%, respectively) or *enantioconvergent* synthesis (8 steps, 37%) from *meso*-tetrahydrophthalic anhydride.



Scheme 2. a) O_3, MeOH, −78°C; H_2O_2, HCOOH, 100°C. b) MeOH, $H^\oplus$, 80°C. c) KO*t*Bu, PhMe, 25°C; 50% H_2SO_4. d) $NaBH_4$, MeOH, −78°C.

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CAS Registry numbers:
5, 88511-03-9; *ent*-**5**, 88586-04-3; *meso*-**6**, 4841-84-3; **7**, 88335-93-7; *ent*-**7**, 88335-94-8; *ent*-**7** · (−)-ephedrine, 88586-05-4; **8**, 65376-03-6; *ent*-**8**, 88586-06-5; **9**, 88586-07-6; *ent*-**9**, 88586-08-7; **10**, 88511-04-0; *ent*-**10**, 88586-09-8; **11a**, 88511-05-1; **11b**, 88586-10-1; **12a**, 88511-06-2; **12b**, 88511-07-3; **13**, 88511-08-4; (1*R*,2*R*)-4-cyclohexene-1,2-dimethanol, 15679-28-4; *meso*-tetrahydrophthalic anhydride, 935-79-5

[1] a) C. Le Drian, A. E. Greene, *J. Am. Chem. Soc. 104* (1982) 5473; b) C. P. Gorst-Allman, P. S. Steyn, C. J. Rabie, *J. Chem. Soc. Perkin Trans. 1 1982*, 2387; c) L. A. Paquette, G. D. Annis, H. Schostarez, *J. Am. Chem. Soc. 104* (1982) 6646; d) P. A. Aristoff, *J. Org. Chem. 46* (1981) 1954; e) W. Skuballa, H. Vorbrüggen, *Angew. Chem. 93* (1981) 1080; *Angew. Chem. Int. Ed. Engl. 20* (1981) 1046.

[2] a) H.-J. Gais, T. Lied, *Angew. Chem. 96* (1984) 143; *Angew. Chem. Int. Ed. Engl. 23* (1984) 145; b) H.-J. Gais, K. L. Lukas, W. Ball, H. Sliwa, 29th IUPAC Congress, Cologne, 1983, Abstr. 215; K. L. Lukas, *Dissertation*, Technische Hochschule Darmstadt 1983; c) H.-J. Gais, *Habilitationsschrift*, Technische Hochschule Darmstadt 1981.

[3] a) The enantioselective saponification of dimethyl *meso*-1,2-hexahydrophthalate with PLE affords the monomethyl ester of (1*S*,2*R*)-1,2-cyclohexanedicarboxylic acid (99%, 80% *ee*) (m.p. = 47—48°C, $[\alpha]_{365}^{20} = +25.0$°C (c = 0.96, EtOH) for ≥99% *ee*) [2c]; b) Additional enantioselective saponifications with PLE: C. S. Chen, Y. Fujimoto, C. J. Sih, *J. Am. Chem. Soc. 103* (1981) 3580, and literature cited therein; M. Arita, K. Adachi, Y. Ito, H. Sawai, M. Ohno, *J. Am. Chem. Soc. 105* (1983) 4049, and literature cited therein.

[4] K.-K. Chen, N. Cohen, J. P. De Noble, A. C. Specian, Jr., G. Saucy, *J. Org. Chem. 41* (1976) 3497; B. M. Trost, J. M. Timko, J. L. Stanton, *J. Chem. Soc. Chem. Commun. 1978*, 436.

[5] The enantioselective oxidation of *meso*-4-cyclohexene-1,2-dimethanol with HLADH/NAD®/FMN offers an alternative route to **8** on the mmol scale (76%, ≥99% *ee*) [6].

[6] I. J. Jakovac, H. B. Goodbrand, K. P. Lok, J. B. Jones, *J. Am. Chem. Soc. 104* (1982) 4659.

Stereoselective Synthesis of (*E*)-4-Hydroxy-2-alkenoic Acid Esters from Aldehydes and the d^3-Building Block Ethyl Lithiopropiolate**

By *Hans-Joachim Gais**

The macrolides brefeldin A **1**[1a], 7-*epi*-brefeldin A **2**[1b], colletodiol **3**[1c], and cytochalasin B **4**[1d] contain an (*E*)-4-hydroxy-2-alkenoic acid structure element. For their *direct* synthesis[2] from aldehydes and building blocks which correspond to the d^3-synthon **5**, there are two methods: the

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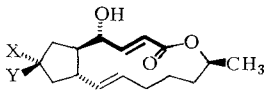
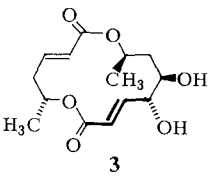
d^3-reagents are either the acid **6**[3] or the vinyllithium compound **7**[4]. In this respect, the stereoselective addition of **6** or **7** to aldehydes was not intended. We describe here an efficient method for the stereoselective synthesis of (*Z*)- and (*E*)-4-hydroxy-2-alkenoic acid esters from aldehydes and the d^3-reagent ethyl lithiopropiolate **8** (Scheme 1) and its application to the *E*/*R*-stereoselective transformation of the aldehyde **14**[5].



1, X = OH, Y = H
2, Y = OH, X = H



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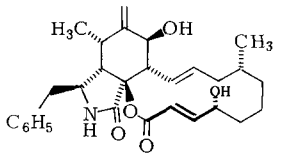

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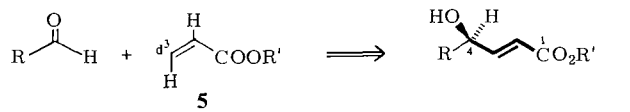

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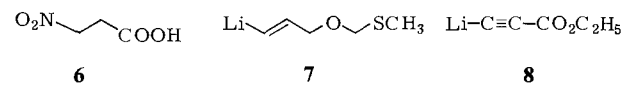


6 **7** **8**

Addition of the lithioalkyne **8**, generated by deprotonation of ethyl propiolate with lithium diisopropylamide in tetrahydrofuran (THF) at −78 °C[6], to the aldehydes **9** proceeds rapidly, even at −78 °C, to yield the alkynes *rac*-**10** (>90%)[7]. The alkynes *rac*-**11** (>90%) are obtained by attaching the methoxyethoxymethyl (MEM), tetrahydropyranyl (THP), *tert*-butyldimethylsilyl (TBDMS), and benzoyl(Bz) groups to *rac*-**10** (R^2 = Li, H). Stereoselective reduction of the alkynoic acids *rac*-**11** (R^3 = H) to the (*E*)-alkenoic acids *rac*-**13** (R^3 = H) is carried out using $CrSO_4$ in dimethylformamide/water at 20 °C[8]; however, complete conversion of *rac*-**11** (R^3 = H) could not be achieved even with an excess of $CrSO_4$. The alkynoic acid esters *rac*-**10** and *rac*-**11** are not reduced under these conditions.

An efficient alternative to the *E*-stereoselective reduction is provided by the two-step method: *Z*-stereoselective hydrogenation and *E*-stereoselective isomerization. The (*Z*)-alkenes *rac*-**12** (>95%, ≥98% *ds*) are accessible by chemo- and stereoselective hydrogenation of the alkynes *rac*-**11**[9]. Structural proof for *rac*-**12** is provided by their ^{1}H-NMR spectra, which in addition to the signals for the *Z*-olefinic protons ($J \approx 12$ Hz) exhibit the signal of H-4, which is shifted to low field by the anisotropic effect of the *syn*-orientated carbonyl group at $\delta = 5.00-5.20$ (Table 1). Subsequent isomerization of the (*Z*)-alkenes *rac*-**12** to the (*E*)-alkenes *rac*-**13** is effected using ca. 30 mol-% $LiSC_2H_5$ in THF at 0–20 °C (>90%). Within the detection limits of ^{1}H-NMR spectroscopy (≥2%), the (*Z*)-alkenes *rac*-**12** were not found. The $LiSC_2H_5$ should not contain HSC_2H_5 impurities, since otherwise the latter undergoes thiolate-catalyzed addition to *rac*-**12** and *rac*-**13**, respectively; in contrast, no addition is observed upon acidic work-up. Apart from signals for the (*E*)-olefinic protons ($J \approx 16$ Hz), the ^{1}H-NMR spectra of *rac*-**13** now exhibit the signal of H-4 at $\delta = 4.02-4.20$, unaffected by the *anti*-orientated carbonyl group (Table 1). Suitable protecting groups for the hydroxy function are the MEM, THP, or TBDMS groups, but not the Bz group since problems then arise in the isomerization step.

Table 1. ^{1}H-NMR data (selected) for *rac*-**12a–c**, *rac*-**13a–c**, **16a**, **b**, and **17a**, **b** (300 MHz, TMS int., δ-values, coupling constants in Hz).

rac-**12a**: 5.05 (H-4, ddd, $J_{3,4}=9$, $J_{4,5}=6$, $J_{2,4}=1$), 5.93 (H-2, dd, $J_{2,3}=12$, $J_{2,4}=1$), 6.14 (H-3, dd, $J_{2,3}=12$, $J_{3,4}=9$) [a].

rac-**12b** (diastereomeric mixture): 5.00 (H-4, ddd, $J_{3,4}=8.5$, $J_{4,5}=5.5$, $J_{2,4}=1$), 5.78 (H-2, dd, $J_{2,3}=12$, $J_{2,4}=1$), 6.08 (H-3, dd, $J_{2,3}=12$, $J_{3,4}=8.5$); 5.12 (H-4, ddd, $J_{3,4}=8.5$, $J_{4,5}=6.5$, $J_{2,4}=0.5$), 5.97 (H-2, dd, $J_{2,3}=12$, $J_{2,4}=0.5$), 6.29 (H-3, dd, $J_{2,3}=12$, $J_{3,4}=8.5$) [a].

rac-**12c**: 5.16 (H-4, ddd, $J_{3,4}=9$, $J_{4,5}=6$, $J_{2,4}=1$), 5.82 (H-2, dd, $J_{2,3}=12$, $J_{2,4}=1$), 6.16 (H-3, dd, $J_{2,3}=12$, $J_{3,4}=9$) [a].

rac-**13a**: 4.02 (H-4, ddd, $J_{3,4}=6.5$, $J_{4,5}=6.5$, $J_{2,4}=1$), 5.95 (H-2, dd, $J_{2,3}=16$, $J_{2,4}=1$), 6.78 (H-3, dd, $J_{2,3}=16$, $J_{3,4}=6.5$) [a].

rac-**13b** (diastereomeric mixture): 4.06 (H-4, ddd, $J_{3,4}=7$, $J_{4,5}=7$, $J_{2,4}=1$), 5.92 (H-2, dd, $J_{2,3}=15.5$, $J_{2,4}=1$), 6.74 (H-3, dd, $J_{2,3}=15.5$, $J_{3,4}=7$); 4.03 (H-4, ddd, $J_{3,4}=6$, $J_{4,5}=6$, $J_{2,4}=1.5$), 6.02 (H-2, dd, $J_{2,3}=15.5$, $J_{2,4}=1.5$), 6.94 (H-3, dd, $J_{2,3}=15.5$, $J_{3,4}=6$) [a].

rac-**13c**: 4.20 (H-4, ddd, $J_{3,4}=5.5$, $J_{4,5}=5.5$, $J_{2,4}=1.5$), 5.97 (H-2, $J_{2,3}=15.5$, $J_{2,4}=1.5$), 6.91 (H-3, dd, $J_{2,3}=15.5$, $J_{3,4}=5.5$) [a].

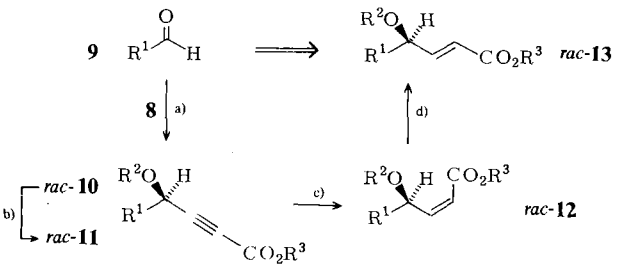
16a: 5.14 (H-4, bdd, $J_{3,4}=8.5$, $J_{4,5}=4.5$, $J_{2,4}=1$), 5.76 (H-2, dd, $J_{2,3}=12$, $J_{2,4}=1$), 6.05 (H-3, dd, $J_{2,3}=12$, $J_{3,4}=8.5$) [b].

16b: 5.20 (H-4, bdd, $J_{3,4}=9$, $J_{4,5}=5$, $J_{2,4}=1$), 5.77 (H-2, dd, $J_{2,3}=12$, $J_{2,4}=1$), 6.12 (H-3, dd, $J_{2,3}=12$, $J_{3,4}=9$) [b].

17a: 4.14 (H-4, m), 5.92 (H-2, bd, $J_{2,3}=15.5$), 6.75 (H-3, dd, $J_{2,3}=15.5$, $J_{3,4}=6$) [b].

17b: 4.14 (H-4, m), 5.94 (H-2, bd, $J_{2,3}=15.5$), 6.79 (H-3, dd, $J_{2,3}=15.5$, $J_{3,4}=7$) [b].

[a] In [D_6]acetone. [b] In $CDCl_3$.



9a–c, *rac*-**10a–c**

a: R^1 = *cyclo*-C_6H_{11}
b: R^1 = *n*-C_8H_{17}–CH=CH–$(CH_2)_7$(*E*)
c: R^1 = *n*-$C_{17}H_{35}$
R^2 = H, R^3 = C_2H_5

rac-**11a–f**, *rac*-**12a–f**, *rac*-**13a–c**

a: R^1 = *cyclo*-C_6H_{11}, R^2 = MEM
b: R^1 = *cyclo*-C_6H_{11}, R^2 = THP
c: R^1 = *cyclo*-C_6H_{11}, R^2 = TBDMS
d: R^1 = *cyclo*-C_6H_{11}, R^2 = Bz
e: R^1 = *n*-C_8H_{17}–CH=CH–$(CH_2)_7$(*E*), R^2 = TBDMS
f: R^1 = *n*-$C_{17}H_{35}$, R^2 = TBDMS
R^3 = C_2H_5

Scheme 1. a) **8**, −78 °C, THF; CH_3COOH, −60 °C. b) MEM-Cl, CH_2Cl_2, $EtN(iPr)_2$; TBDMS-Cl, dimethylformamide, imidazole or Bz-Cl, pyridine for R^2 = H and MEM-Cl or Bz-Cl for R^2 = Li. c) H_2, Pd/$BaSO_4$, quinoline, CH_3OH, 760 torr, 25 °C. d) $LiSC_2H_5$, THF, 0–20 °C, 1 h; 0.1 N HCl, 0 °C.

The potential of this method is demonstrated by the conversion of the aldehyde **14** [$[\alpha]_D^{20}$ −25.9 (1.29, CH_2Cl_2)] via **15a**, **b** and **16a**, **b** into a 4:1 mixture of the 7-*epi*-brefeldin A seco-acid esters **17a**, **b** [$[\alpha]_D^{20}$ −31.9 (1.82, ethyl acetate) for R = H] (**14** → **17a**, **b**: 75%). The diastereoselectivity of the addition of **8** to **14** is 80% (**a** : **b** = 4 : 1), as determined by ^{1}H-NMR spectroscopy and by chromatographic separation of the isomers **15** (**a**: X = OH, Y = H,

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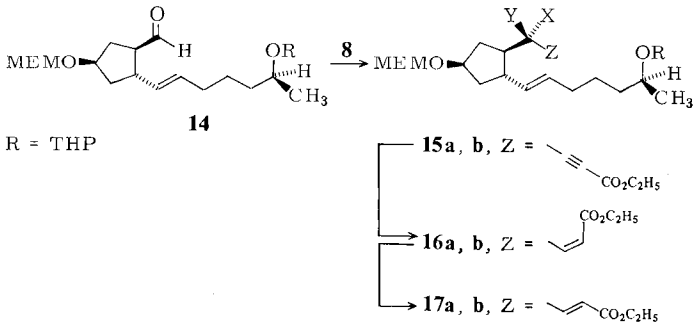

a: X = OMEM, Y = H; **b**: Y = OMEM, X = H

R=H; **b**: Y=OH, X=H, R=H). The configurations of **17a** and **17b** (4:1) were assigned by conversion into **2** and 4-*epi*-**2** (4:1)[5], respectively.

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CAS Registry numbers:
2, 83710-00-3; 4-*epi*-**2**, 88586-99-6; **8**, 72036-30-7; **9a**, 2043-61-0; **9b**, 10009-79-7; **9c**, 638-66-4; (±)-**10a** (R^2=H), 88525-82-0; (±)-**10a** (R^2=Li), 88525-85-3; (±)-**10b**, 88525-83-1; (±)-**10c**, 88525-84-2; (±)-**11a**, 88525-86-4; **11b**, 88525-87-5; (±)-**11c**, 88525-88-6; (±)-**11d**, 88525-89-7; (±)-**11e**, 88525-90-0; (±)-**11f**, 88525-91-1; (±)-**12a**, 88525-92-2; (*R*,S**)-(±)-**12b**, 88525-93-3; (*R*,R**)-(±)-**12b**, 88526-04-9; (±)-**12c**, 88525-94-4; (±)-**12d**, 88525-95-5; (±)-**12e**, 88525-96-6; (±)-**12f**, 88525-97-7; (±)-**13a**, 88525-98-8; (*R*,S**)-(±)-**13b**, 88525-99-9; (*R*,R**)-(±)-**13b**, 88526-05-0; (±)-**13c**, 88526-00-5; **14**, 88526-01-6; **15a**, 88526-02-7; **15b**, 88586-95-2; **16a**, 88526-03-8; **16b**, 88586-96-3; **17a**, 88586-97-4; **17b**, 88586-98-5; MEM-Cl, 3970-21-6; TBDMS-Cl, 18162-48-6; Bz-Cl, 98-88-4; $LiSC_2H_5$, 30383-01-8

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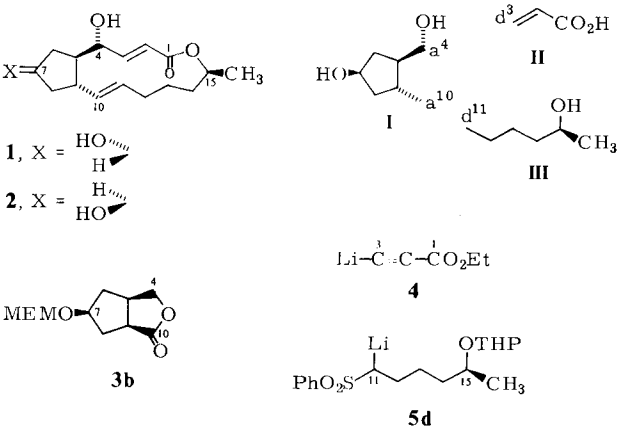
Asymmetric Total Synthesis of the Macrolides Brefeldin A and 7-*epi*-Brefeldin A**

By *Hans-Joachim Gais** and *Thomas Lied*

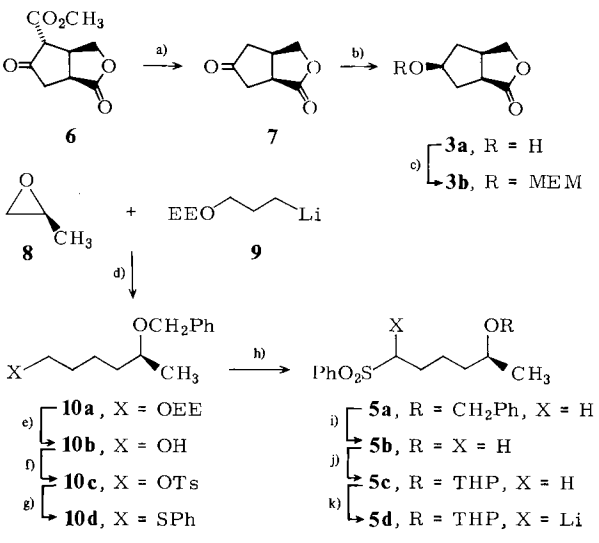
Because of their interesting structures, which resemble those of the prostaglandins, and unusually broad spectrum of interesting biological activity, the macrolides brefeldin A **1**[1a,b] and 7-*epi*-brefeldin A **2**[1c], biosynthesized by *Curvularia lunata*, are attractive target molecules for chemical synthesis[1d]. In 1981 we prepared the intermediate 7-*epi*-**14** (tBuMe$_2$Si for THP)[2], formally the first asymmetric total synthesis of **1**[3a,b]; later, a second asymmetric total synthesis was described[1d]. Here, we report a novel asymmetric total synthesis of **1** and the first of **2**, in which we employ new methods for the stereoselective construction of the C1-C4 structure element and for the macrolactonization. Our synthetic strategy can be deduced from the synthons **I**—**III**; in their connection sequence, the corresponding building blocks are the cyclopentanolactone **3b**, the lithiosulfone **5d**, and the lithiopropiolate **4** (Scheme 1).



Scheme 1. MEM=(2-methoxyethoxy)methyl, THP=2-tetrahydropyranyl.

The synthesis of the cyclopentanoid building block **3b** commences with the cleavage of the β-keto ester **6** (≥99% *ee*)[4] to afford the bicyclic ketone **7**[5a] (96%)[6], which after catalytic hydrogenation yields the β-alcohol **3a**[5b] (97%, 98% *ds*), and which is subsequently protected as the MEM ether **3b**[5c] (91%, ≥99% *ee*) (Scheme 2).

Regioselective ring-opening of (*S*)-propylene oxide **8** (97% *ee*)[7] with the organolithium compound **9** (EE=1-ethoxyethyl)[8] leads via the alcohol **10b**[5d] and the sulfide **10d**[5e] to the sulfone **5c**[5f] (50% overall yield, 97% *ee*)[9] (Scheme 2).



Scheme 2. a) Me_2NCHO, H_2O, NaCl, 120°C. b) H_2, Pd/C, $MeCO_2Me$. c) MEM-Cl, CH_2Cl_2, $EtN(iPr)_2$. d) Tetrahydrofuran (THF), −30°C; $PhCH_2Br$. e) $H^\oplus$, H_2O. f) TsCl, pyridine. g) LiSPh, THF, 25°C. h) *m*-Cl−C_6H_4−CO_3H, $CHCl_3$, −10°C. i) H_2, Pd/C, MeOH. j) Dihydropyran, $H^\oplus$. k) *n*BuLi, THF, −78°C.

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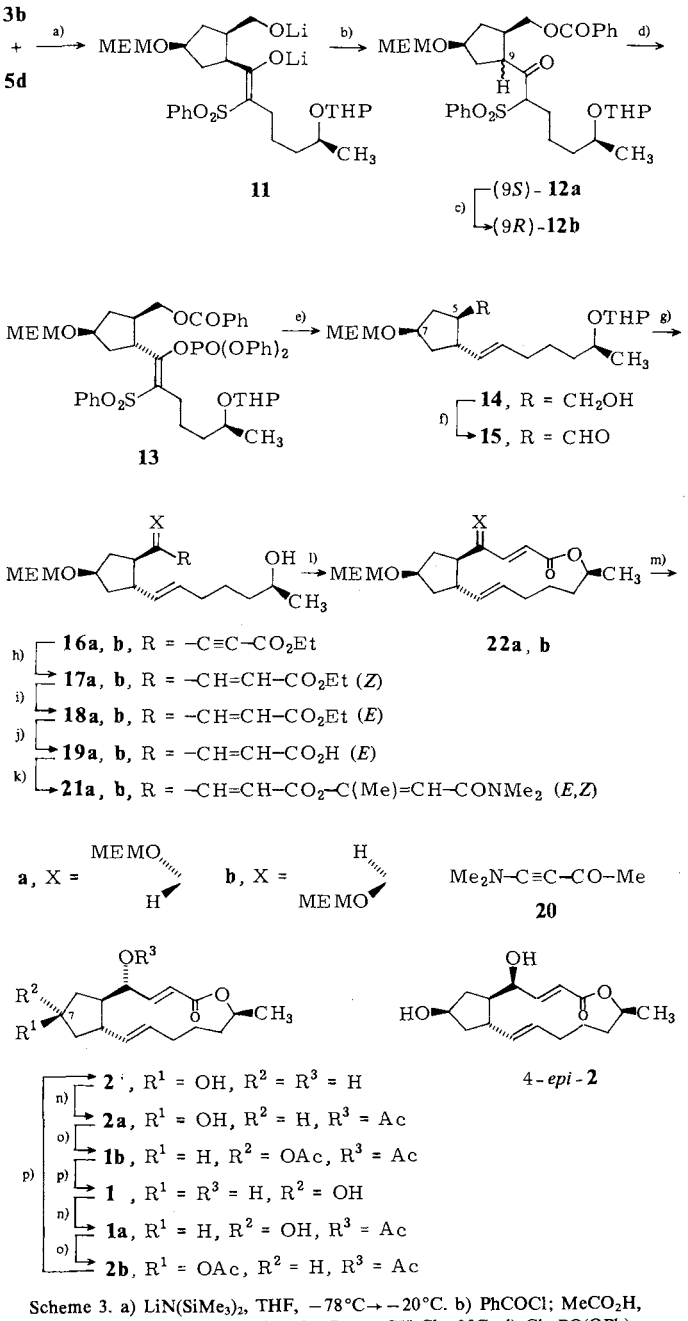
The C4–C10 building block **3b** is linked smoothly in three steps to the C11–C16 building block with the correct configuration at C9: ring-opening of the lactone **3b** with the lithiosulfone **5d** to give the dilithio compound **11** and chemoselective benzoylation; the initially formed (9*S*)-keto sulfone **12a** is isomerized to the more stable (9*R*)-keto sulfone **12b**[5g] (≥30:1) (Scheme 3). **12b** (90% overall yield) is converted into the enol phosphate **13**[5h] (94%), which was reduced to the (*E*)-alkene **14**[5i] (76%)[10] with concomitant release of the hydroxymethyl function. Oxidation of the alcohol **14** to the aldehyde **15**[5j] (87%) completes the requirements for the coupling of the still absent C1–C3 structure element. A novel, potent method for this[11] starts with the *re*-selective addition of **4** to **15**, which affords, via the alkynes **16**[5k] (90%, 80% *ds*) and the (*Z*)-alkenes **17**[5l] (92%), the (*E*)-alkenes **18**[5m] (91%). Saponification of **18** leads to the seco-acids **19**[5n] (94%), which were lactonized using a novel, efficient method[12]: chemoselective reaction of **19** with the "push-pull" alkyne **20**[13] to give the stable enol esters **21**[5o] (96%) and their $H^{\oplus}$-catalyzed cyclization to the macrolides **22**[5p] (74%) (Scheme 3). These are cleaved to furnish **2** and 4-*epi*-**2** (4:1, 83%), which are separated readily by chromatography. Inversion of the configuration at C 7 of **2a**, prepared by selective acylation of **2**[1c], according to *Mitsunobu*[14], and cleavage of the diacetate **1b** thus obtained lead to **1**. Similarly, the synthesis of **2** from **1** can be carried out via **1a**[1b] and **2b**[1c]. The flexibility of this synthetic strategy for **1** and **2** permits use of the equally readily accessible *ent*-**3b**[4] as educt instead of **3b**, and now with the inversion of configuration 5,7-*epi*-**15**→7-*epi*-**15** leads primarily to **1**. The macrolides brefeldin A **1** [m.p. = 203 °C, $[\alpha]_D^{20}$ +92.1 (0.25, MeOH)] and 7-*epi*-brefeldin A **2** [m.p. = 121–123 °C, [α] +109.6 (0.19, MeOH)] thus obtained are indistinguishable both chromatographically and spectroscopically (300 MHz ^{1}H-NMR) from **1** obtained from *Penicillium brefeldianum* and **2** from *Curvularia lunata*.



Scheme 3. a) $LiN(SiMe_3)_2$, THF, −78 °C→−20 °C. b) PhCOCl; $MeCO_2H$, 0 °C. c) 1,8-Diazabicyclo[5.4.0]undec-7-ene, CH_2Cl_2, 0 °C. d) Cl–$PO(OPh)_2$, MeCN, NEt_3, 4-dimethylaminopyridine. e) Na, NH_3, −78 °C. f) Pyridinium chlorochromate, CH_2Cl_2, 0 °C. g) **4**, THF, −78 °C; MEM-Cl, −78 °C→0 °C; MeOH, $H^{\oplus}$. h) H_2, Pd/$BaSO_4$, quinoline, MeOH. i) LiSEt, THF, 30 °C; 0.1 N HCl, 0 °C. j) LiOH, MeOH; 0.1 N HCl, 0 °C. k) **20**, THF, 0 °C. l) 5 mol-% 10-camphersulfonic acid, PhMe, 80 °C, dilution. m) $TiCl_4$, CH_2Cl, 0 °C. n) Ac_2O, pyridine. o) Ph_3P, diethyl azodicarboxylate, $MeCO_2H$, THF, 0 °C. p) MeOH, K_2CO_3, 0 °C.

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1, 20350-15-6; **1a**, 83710-02-5; **1b**, 29129-37-1; **2**, 83710-00-3; 4-*epi*-**2**, 88586-99-6; **2a**, 83692-17-5; **2b**, 83710-01-4; **3a**, 88587-00-2; **3b**, 88526-06-1; **4**, 72036-30-7; **5a**, 88526-07-2; **5b**, 88526-08-3; **5c**, 88526-09-4; **5d**, 88526-10-7; **6**, 88526-11-8; **7**, 88587-01-3; **8**, 16088-62-3; **9**, 37494-03-4; **10a**, 88526-12-9; **10b**, 88526-13-0; **10c**, 88526-14-1; **10d**, 88526-15-2; **11**, 88526-16-3; **12a**, 88526-17-4; **12b**, 88587-02-4; **13**, 88526-18-5; **14**, 88526-19-6; **15**, 88526-01-6; **16a**, 88526-20-9; **16b**, 88587-03-5; **17a**, 88526-21-0; **17b**, 88587-04-6; **18a**, 88587-05-7; **18b**, 88587-06-8; **19a**, 88587-07-9; **19b**, 88587-08-0; **20**, 20568-22-3; **21a**, 88588-18-5; **21b**, 88526-22-1; **22a**, 88587-09-1; **22b**, 88588-19-6

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[5] a) M.p. = 84 °C, $[\alpha]_D^{20}$ −67.8 (*c* = 2.59, CH_2Cl_2); b) m.p. = 71 °C, $[\alpha]_D^{20}$ +61.2 (2.64, CH_2Cl_2); c) m.p. = 48 °C, $[\alpha]_D^{20}$ +21.1 (1.86, CH_2Cl_2); d) $[\alpha]_D^{20}$ +26.5 (1.00, $CHCl_3$); e) $[\alpha]_D^{20}$ +18.9 (2.86, CH_2Cl_2); f) $[\alpha]_D^{20}$ +7.7 (3.90, EtOH); g) $[\alpha]_D^{20}$ −13.5 (1.00, CH_2Cl_2); h) $[\alpha]_D^{20}$ −12.5 (1.70, CH_2Cl_2); i) $[\alpha]_D^{20}$ −11.1 (1.02, CH_2Cl_2); j) $[\alpha]_D^{20}$ −25.9 (1.29, CH_2Cl_2); k) $[\alpha]_D^{20}$ −6.1 (1.73, ethyl acetate) for **a** : **b** = 4 : 1; l) $[\alpha]_D^{20}$ −11.8 (1.62, ethyl acetate) for **a** : **b** = 4 : 1; m) $[\alpha]_D^{20}$ −31.9 (1.82, ethyl acetate) for **a** : **b** = 4 : 1; n) $[\alpha]_D^{20}$ −27.8 (1.88, THF) for **a** : **b** = 4 : 1; o) $[\alpha]_D^{20}$ −28.7 (2.00, CH_2Cl_2) for **a** : **b** = 4 : 1; p) $[\alpha]_D^{20}$ +8.6 (1.19, ethyl acetate) for **a** : **b** = 4 : 1.

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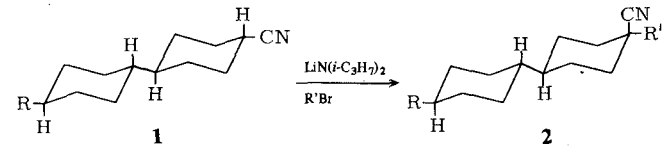
Liquid-Crystalline 4-Bicyclohexylcarbonitriles with Extraordinary Physical Properties

By *Rudolf Eidenschink**, *Günther Haas*, *Michael Römer*, and *Bernhard S. Scheuble*

Liquid-crystalline 4-(*trans*-4-alkylcyclohexyl)benzonitriles[1] and 4'-alkyl-4-bicyclohexylcarbonitriles **1**[2] have achieved considerable importance in display technology. We have now found that 4α,4'α-dialkyl-1α,1'α-bicyclohexyl-4β-carbonitriles **2** also exhibit surprisingly high transition temperatures for conversion from the nematic to the isotropic states (T_{NI}) (Table 1). Compounds **2** were synthesized by the reaction of **1** with an alkyl bromide and lithium diisopropylamide at −50°C in tetrahydrofuran in the molar ratios shown, a variation of a previously described alkylation method[3]. The crude products were purified by column chromatography (silica gel 60, Merck/toluene) and recrystallization from ethanol: yields are between 60 and 70%. The structures are corroborated by elemental analyses and by mass and ^{13}C-NMR spectra[4].



1 **2**

Table 1. Transition temperatures for some 4α,4α'-di-*n*-alkyl-1α,1α'-bicyclohexyl-4β-carbonitriles **2**. C = crystalline, S = smectic, N = nematic, I = isotropic phases.

2	R	R'	T_{CS} [°C]	T_{SN} [°C]	T_{NI} [°C]
a	C_3H_7	C_3H_7	32		(17)
b	C_3H_7	C_5H_{11}	40		49
c	C_3H_7	C_7H_{15}	22	(16)	56
d	C_4H_9	C_4H_9	9	30	38
e	C_5H_{11}	C_5H_{11}	24	(24)	66
f	C_7H_{15}	C_3H_7	38	39	49

The liquid-crystalline, specifically the nematic, behavior of compounds **2** having *axial* CN groups was not predicted by a model[5] which—based on the intermolecular interactions known from the theory of liquids[6]—suggests an association of lengthwise-extended molecular pairs via *equatorial* CN groups arranged in an antiparallel fashion as explanation for the high T_{NI} values of compounds **1**. Also the present findings require that statements correlating chemical structure and T_{NI} be revised[7]. As in **1**[2], smectic phases also occur in **2** (Table 1), however, at comparably lower temperatures.

Clearly, the axial CN groups in **2** are well shielded by the H atoms at the 2- and 6-positions as well as by the geminal alkyl groups. Since the anisotropy of the dielectric constant ($\Delta\varepsilon$)[8] at 20°C lies between −8 and −10 (in **1** with equatorial CN groups, $\Delta\varepsilon$ is +4 to +5), it can be concluded that in **2** the conformation with axial CN groups is largely preferred. Measurement of the (CH) coupling constants[4] confirm this assumption. Because of their $\Delta\varepsilon$ values, stability, and optical anisotropy (birefringence $\Delta n \approx 0.03$), compounds **2** may be of specific interest for electrooptical displays based on the alignment of dichroitic dyes in liquid-crystalline matrices[9].

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1 (R = C_3H_7), 65355-35-3; **1** (R = C_4H_9), 70784-10-0; **1** (R = C_5H_{11}), 65355-36-4; **1** (R = C_7H_{15}), 65355-37-5; **2a**, 88510-85-4; **2b**, 88510-86-5; **2c**, 88510-87-6; **2d**, 88510-88-7; **2e**, 88510-89-8; **2f**, 88510-90-1; LiN(*i*-C_3H_7)$_2$, 4111-54-0; C_3H_7Br, 106-94-5; $C_5H_{11}Br$, 110-53-2; $C_7H_{15}Br$, 629-04-9; C_4H_9Br, 109-65-9

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Aliphatic Polyethers, Basic Building Blocks from Naturally Occurring Humic Substances: Detection by Solid State ^{13}C-NMR Spectroscopy**

By *Ernst Bayer**, *Klaus Albert*, *Wolf Bergmann*, *Kuno Jahns*, *Wolfram Eisener*, and *Hans-Konrad Peters*

Although approximately 60×10^{11} t of organically bound carbon occurs as humic substances[1,2], the structure of these natural products still represents a puzzle. Humic substances contain C, H, and O. The high oxygen content, which leads, according to the age of the humic substance, to a C:O ratio of between 1.6 in recently formed humic substances from waters to 2.5 in the oldest humic acids (lignites) could not be accounted for by previous structural proposals; it is assumed that humic substances contain structural elements predominantly derived from arenes[3]. Since humic substances are often sparingly soluble and alkaline extraction methods can produce changes in the humic acids, non-destructive, structure determining methods have to be resorted to. Cross polarization-magic angle spinning CP-MAS-^{13}C-NMR spectroscopy[4] has recently permitted the exact assignment of the structural elements of solid-state samples.

We have now found that the position of the principal signals in the solution and solid-state ^{13}C-NMR spectra is the same (Fig. 1)[5]. This finding permits reliable statements to be made about the structure of humic substances in the solid state. In contrast to previous hypotheses about the structure, only very weak signals in the arene region ($\delta = 120-160$) occur in both solution and solid-state spectra. Instead, very intense signals from the saturated, aliphatic hydrocarbon chains ($\delta = 10-40$) are observed. Hence, in humic substances from waste water aliphatic structures dominate the basic structure and not aromatics. Intense signals occur at $\delta = 70$ for oxygen containing groups; these can be assigned to the structural element −CHR−O−CHR. In addition, signals arising from ester or carboxy groups ($\delta = 175$) and for acetals ($\delta = 100$) occur in the assigned part of the spectra. Presumably, aliphatic ether groups are the linking structural principle in humic acids; basic building blocks could be polyethers of glycols, e.g. of glycerol. This is also confirmed by the IR spectra (signals in the region of 1120 cm^{-1}). Assuming that the

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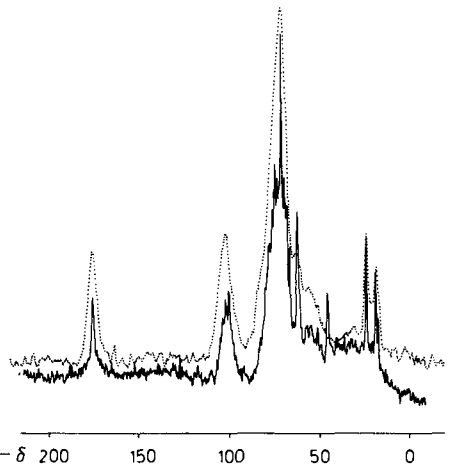

Fig. 1. ^{13}C-NMR spectrum (100.6 MHz) from waste-water humic substances in D_2O solution (—); CP-MAS-^{13}C-NMR spectrum (50.3 MHz) of the same solid waste-water humic substance (....).

ether C atoms and non-functionalized, aliphatic C atoms have similar correlation times, the signal intensity suggests that every second C atom participates in an ether bond. The ether groups should at least be partially hydrolyzable, even if the chemical sluggishness and reduced accessibility in the cross-linked, polymeric humic substances is considered[6]. The signals assigned to the ether C atoms almost completely disappear when the solutions are treated several times with excess 57% boiling hydriodic acid.

Do the part-structures found in waste water humic acids also occur in humic substances from different origins? Previously described NMR spectra of such humic substances suggest this[7]; however, because of the low resolution, weak signals, and possible structural changes caused by the method of isolation, the results are often difficult to interpret[8,9].

In order to avoid structural changes arising from the method of isolation, we initially recorded solid-state spectra of peat. The overlap of the spectrum of the humic acid by that of lignin produces no interference since the latter does not exhibit signals of aliphatic ether groups and aliphatic side chains at $\delta = 70$ and 10—40, respectively[10,11].

The CP-MAS-^{13}C-NMR spectrum of a sample of peat shows the same characteristic signals as the spectra of waste water humic acids (Fig. 2, top). In addition, signal groups typical for lignins at $\delta = 100$—500 (aryl moieties) occur together with a signal for the OCH_3 group at $\delta = 55$. Also for peat—despite the lignin—predominantly aliphatic structural elements occur. A soil humic acid also exhibits a similar solid-state spectrum to that of peat (Fig. 2, middle)[12]; the ether bonds can be cleaved with HI. The structural elements of humic substances from waste water systems, peat, and soils are therefore similar.

In the CP-MAS-^{13}C-NMR spectrum of a humic acid isolated from lignite using caustic soda (Fig. 2, bottom) the signals of the functional groups are much weaker than those of the aliphatic residues ($\delta = 10$—50); however, both the ether and carboxy groups are clearly recognizable. The functionalized C atoms in the humic acids which are relatively young on the geological time scale are apparently converted into alkyl residues as they age (conversion into lignite).

This is interesting since humic substances have been discussed as connecting links in the genesis of fossil fuels[13]. It was never completely understood how humic substances, made up predominantly of aromatic structural elements, could be converted into the aliphatics found almost exclusively in petroleum under the relatively mild conditions associated with its formation. Since the aliphatic structural elements present in humic substances cannot be further degraded microbiologically, this forms the basis for aliphatic geopolymers and petroleum. The greater amount of aromatic structures in coal may therefore arise from products of lignin degradation and not from humic substances. This point of view is also consistent with the various starting substrates for the genesis of petroleum and coal[13]. Petroleum is predominantly formed from lignin-free aquatic biomass[14], and coal from lignin-containing biomass of vegetable origin.

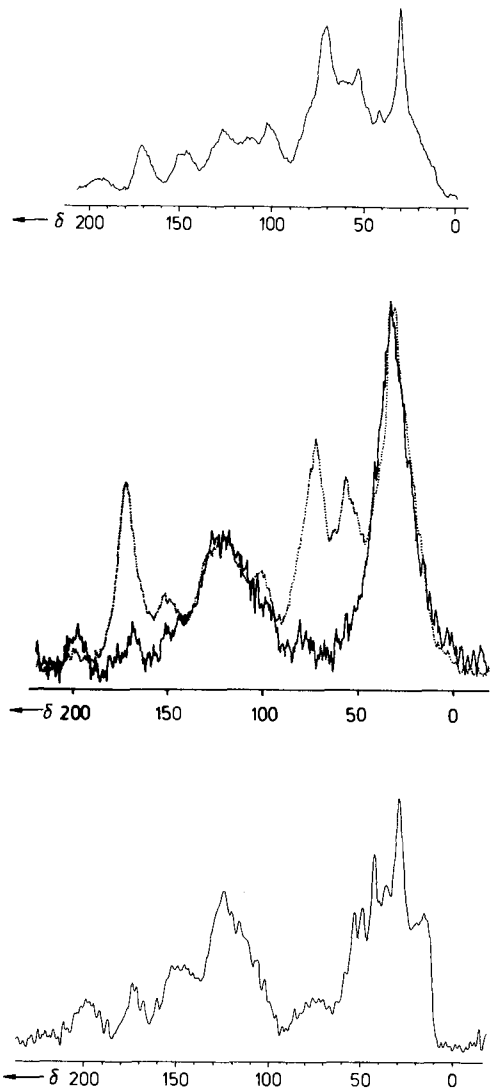

Fig. 2. Top: CP-MAS ^{13}C-NMR spectrum (50.3 MHz) of solid peat (peat bog, Aha/Kreis Rosenheim, FRG).—Middle: CP-MAS-^{13}C-NMR spectra (50.3 MHz) of soil humic acid, before (.....) and after treatment with 57% hydriodic acid (———).—Bottom: CP-MAS ^{13}C-NMR spectrum (50.3 MHz) of solid humic acid from Rhenish lignite.

Summarizing our results therefore suggests that 1) the fundamental framework of these natural products form aliphatic structural elements, and 2) that among the oxygen-containing functional groups the aliphatic ethers assume a dominant position. No statement can be made yet about a total structure. The bacterial sludge obtained from the aerobothermophilic degradation of sewage sludge is particularly suitable for the isolation of humic substances. Ex-

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traction of this bacterial sludge with water, several precipitations, and membrane filtration lead to isolation of humic substances in over 10% yield (relative to the degraded organic substances). Pure cultures of such thermophilic bacteria could be a route to more homogeneous humic acid preparations.

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$(Ph_4As)_2[Cl_5W(\mu\text{-}N_4)WCl_5]$, a μ-Isotetrazenido(4−) Complex of Tungsten(VI)

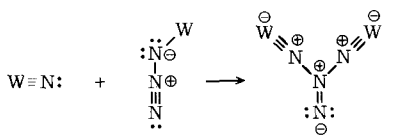
By *Werner Massa, Richard Kujanek, Gerhard Baum,* and *Kurt Dehnicke**

The terminal nitrido ligand in $L_nM{\equiv}N$: transition metal complexes has weakly basic properties and thus often leads to stretched $M{\equiv}N{-}M$ bridge bonding with various M−N bond lengths on complexation[1]. Nitrido complexes are usually synthesized by thermolysis of azido complexes[1,2]. We have now found that the nitride formed in one of these reactions reacts with azide that is still present with formation of the previously unknown tetraanionic isotetrazene bridge ligand:

$$2\,Ph_4AsCl + W(N)Cl_3 + W(N_3)Cl_5 \longrightarrow (Ph_4As)_2[Cl_5W(\mu\text{-}N_4)WCl_5]$$

The binuclear tungsten complex can be isolated as the salt in the form of red single crystals from dichloromethane in the presence of tetraphenylarsonium chloride.

According to the X-ray structure analysis[3] the two WCl_5 groups in the complex anion (Fig. 1) are linked via very short WN bonds (Table 1) with the bridging planar N_4 moiety. This probably arises by nucleophilic attack of the nitrido ligand at the β-N atom of an azido ligand.



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The N atom thus attacked becomes sp^2 hybridized (bond angle of 109 to 126° at N2, cf. Table 1). The markedly long N1−N2 and N2−N4 bonds signalize the easy cleavability of a N_2-molecule (N2N3); the N2−N3 bond length of 123 pm corresponds to that of a double bond.

In agreement with the structural findings, the IR spectrum shows a band at 1640 cm^{-1} for ν(N=N)—characteristic for a double bond[6]. Two bands occur at 1224 and 1245 cm^{-1} for $\nu(W{\equiv}N)$, which are assigned to the somewhat different $W{\equiv}N{-}N$ groups; their short-wave position can be ascribed to strong coupling with ν(N−N)[1,6].

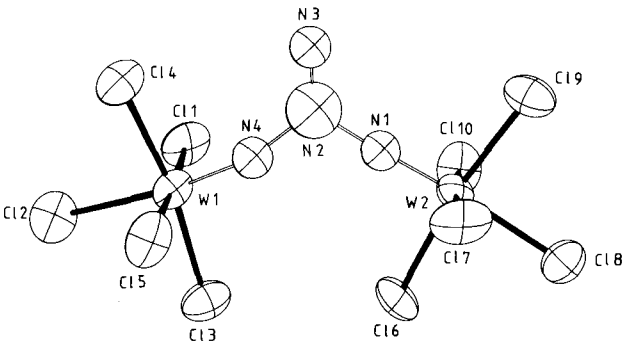

Fig. 1. ORTEP diagram of the $[Cl_5W(\mu\text{-}N_4)WCl_5]^{2\ominus}$ anion in the crystal of the tetraphenylarsonium salt (vibration ellipsoids with 50% probability).

Table 1. Important bond lengths [pm] and angles [°].

W1−N4	165(1)	W1−N4−N2	164(1)
W2−N1	162(1)	W2−N1−N2	177(1)
N2−N4	148(2)	N1−N2−N4	109(1)
N2−N1	150(2)	N1−N2−N3	126(1)
N2−N3	123(2)	N4−N2−N3	125(2)
W1−Cl2	242.3(4)	N4−W1−Cl(1,3,4,5)	93.9(4) [a]
W1−Cl(1,3,4,5)	232.7(4) [a]	N1−W2−Cl(6,7,9,10)	94.4(4) [a]
W2−Cl8	244.8(4)	N4−W1−Cl2	170.0(4)
W2−Cl(6,7,9,10)	232.4(4) [a]	N1−W2−Cl8	175.8(3)

[a] Mean value.

The novel bridge ligand can be regarded as a fourfold deprotonated isotetrazene, which is isosteric with urea and, in contrast to the well investigated tetrazene, H_2NNNNH_2[4,5], is still unknown.

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[4] N. Wiberg, H.-W. Häring, S. K. Vasisht, *Z. Naturforsch. B 34* (1979) 356.
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Trifluoroethylidynesulfur Trifluoride, $F_3C-C{\equiv}SF_3$**

By *Brigitte Pötter* and *Konrad Seppelt**

The carbon-sulfur bond in $H_2C{=}SF_4$[1] can be characterized as a weakly polar, genuine double bond; a corresponding triple bond should therefore exist. However, the synthesis of $HC{\equiv}SF_3$ from $H_2C{=}SF_4$ or from another precursor has not been achieved so far, although its existence was confirmed by ab initio calculation[2] and its analogy to $N{\equiv}SF_3$ argues in its favor. Elimination of HF from $H_2C{=}SF_4$ led, in all previous attempts, directly to $S{=}CF_2$[1].

$$H_2C{=}SF_4 \xrightarrow[-HF]{} \{HC{\equiv}SF_3\} \xrightarrow[-HF]{} S{=}CF_2$$

It should be possible to prevent the second elimination step by straightforward substitution at the methylene group. Recently, the substituted compounds $H_3C-CH{=}SF_4$[3] and $F_3C-CH{=}SF_4$[4] have become available, e.g.

$$ROC{\equiv}CH + ClSF_5 \xrightarrow{h\nu} RO-CCl{=}CH-SF_5$$
$$\xrightarrow{Br_2} RO-CClBr-CHBr-SF_5 \xrightarrow[-RBr]{\Delta} OCCl-CHBr-SF_5$$
$$\xrightarrow{H_2O} HOOC-CHBr-SF_5 \xrightarrow{SF_4/HF} F_3C-CHBr-SF_5$$
$$\xrightarrow[-110\,^\circ C]{C_5H_{11}Li} F_3C-CH{=}SF_4$$

The trifluoromethyl derivative eliminates HF practically quantitatively if pumped in the gaseous state at 50–60 °C and 10^{-1} mbar through a 40 cm long quartz tube (12 mm diameter, packed with powdered, dried KOH).

$$F_3C-CH{=}SF_4 \xrightarrow[-HF]{KOH} F_3C-C{\equiv}SF_3$$

The product $F_3C-C{\equiv}SF_3$ is a colorless gas, m.p. = −122 °C, b.p. = −15 to −10 °C (rapid oligomerization). Its composition was determined by high-resolution mass spectroscopy (*m/z* 169.96271, M^+, 13.2%, theor. 169.96250, and numerous smaller fragments).

The isomers $FC{\equiv}C-SF_5$, $F_2C{=}C{=}SF_4$, $F_3C-CF{=}\ddot{S}F_2$, and $F_2C{=}CF-\ddot{S}F_3$ are precluded by the ^{19}F-NMR spectrum: In accord with the structure $F_3C-C{\equiv}SF_3$, two similar quartets are observed in the SF region ($\delta = 65.7$) and in the CF region ($\delta = -43.9$), $J_{F-F} = 19.5$ Hz. The first information about the nature of the carbon-sulfur bond is provided by the IR gas spectrum: In addition to the typical CF and SF stretching vibrations at 1225, 1168, 862, and 730 cm^{-1}, a strong, very broad band occurs at 1740 cm^{-1}, which because of its high absorption frequency can be unequivocally assigned to the CS triple bond. This bond lies ca. 225 cm^{-1} higher than that of the NS triple bond in $N{\equiv}SF_3$, indicating a particularly high bond order in $F_3C-C{\equiv}SF_3$[5]. More details on the molecular structure would result from a complete force field analysis.

The novel compound $F_3C-C{\equiv}SF_3$ does not achieve the extraordinary stability of $F_3C-CH{=}SF_4$, and oligomerizes to a product which is liquid at room temperature but crystalline at low temperatures (according to preliminary NMR results this could be a cyclic dimer).

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CAS Registry numbers:
$F_3CCH{=}SF_4$, 88476-02-2; $F_3CC{\equiv}SF_3$, 88476-03-3

[1] G. Kleemann, K. Seppelt, *Angew. Chem.* 90 (1978) 547; *Angew. Chem. Int. Ed. Engl.* 17 (1978) 516; *Chem. Ber.* 116 (1983) 645.
[2] V. Bonačič-Koutecký, unpublished.
[3] B. Pötter, K. Seppelt, *Inorg. Chem.* 21 (1982) 3147.
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A New Route to Iron-Sulfur Clusters: Synthesis and Structure of $[(C_2H_5)_4N]_2Fe_6S_6I_6$**

By *Wolfgang Saak, Gerald Henkel,* and *Siegfried Pohl**

The importance of iron-sulfur complexes as models for the active centers in non-heme iron proteins has excited interest in the last few years in the synthesis of a series of clusters of varied structures[1,2]. During investigations of the iron-sulfur-iodine system we found a novel route to iodine-substituted Fe–S clusters, starting from the elements and tetraethylammonium iodide.

We report here on the novel cluster anion $Fe_6S_6I_6^{2\ominus}$, which can be formally synthesized according to

$$6\,Fe + 6\,S + 2\,I_2 + 2\,I^{\ominus} \longrightarrow [Fe_6S_6I_6]^{2\ominus}$$

and isolated as $(Et_4N)_2Fe_6S_6I_6$ **1**[3]. The formation of the complex dianion probably proceeds *via* lower charged species which are readily soluble in CH_2Cl_2 and which so far have never been isolated[3].

According to the X-ray structure analysis of **1** discrete $Fe_6S_6I_6^{2\ominus}$ ions are present in the salt, which, with a symmetry approaching D_{3d}, have C_i crystal symmetry. The hitherto unknown Fe_6S_6 moiety[4] in the series of iron-sulfur clusters consists of two chair-shaped Fe_3S_3 rings which are coupled via six Fe–S bonds (Fig. 1). The three symmetry-independent Fe atoms have almost the same, approximately tetrahedral environment. Hence the formal oxidation number for all iron atoms is +2.67 (bond lengths: Fe–S 224.4(4)–227.1(5), Fe–Fe 271.8(3)–276.4(3), Fe–I 251.8(2)–254.9(2) pm; in each case the shortest bonding contacts in the cluster are given).

The μ_3-S atoms are also similarly coordinated. However, in contrast to the Fe–S–Fe angles in the Fe_4S_4 moiety[5], those in **1** are markedly different (for all three symmetry-independent S atoms: two Fe–S–Fe angles between

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73.8(1) and 75.1(1)°, the third between 112.6(2) and 116.3(2)°); the atomic array in **1** rather resembles that of μ_4-sulfur, with the fourth coordination site missing.

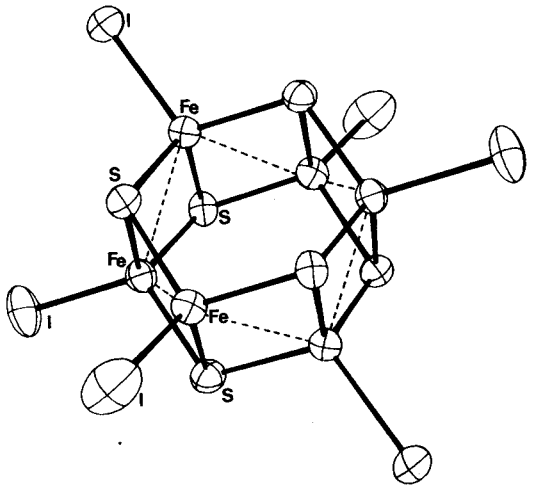

Fig. 1. Structure of the $Fe_6S_6I_6^{2\ominus}$ anion in the crystal of **1** (shortest Fe–Fe contacts shown with dotted lines). Structural data: $P2_1/n$, $a = 802.9(1)$, $b = 1334.1(2)$, $c = 2045.5(3)$ pm, $\beta = 100.04(1)°$, $Z = 2$; 3401 symmetry independent reflections, 2031 observed ($I > 3\sigma(I)$); empirical absorption correction; $R = 0.049$. Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen, on quoting the depository number CSD 50661, the names of the authors, and full citation of the journal.

Depending on the molar ratio of the reactants, further Fe–S–I clusters should be accessible via the synthetic route described for **1**. Thus we were also able to prepare and structurally characterize in an analogous way the complexes $Fe_2S_2I_4^{2\ominus}$ and $Fe_4S_4I_4^{2\ominus}$[7], which had already been synthesized via an alternative route[6].

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CAS Registry numbers:
1, 88610-35-9; Fe, 7439-89-6; I, 7553-56-2; S, 7704-34-9

[1] Cf. e.g. T. Herskovitz, B. A. Averill, R. H. Holm, J. A. Ibers, W. D. Phillips, J. F. Weiher, *Proc. Natl. Acad. Sci. USA 69* (1972) 2437; K. S. Hagen, J. M. Berg, R. H. Holm, *Inorg. Chem. Acta 45* (1980) L17; G. Christou, R. H. Holm, M. Sabat, J. A. Ibers, *J. Am. Chem. Soc. 103* (1981) 6269; K. S. Hagen, A. D. Watson, R. H. Holm, *ibid. 105* (1983) 3905.

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[3] Procedure (all operations performed under nitrogen in dry, oxygen-free solvents): A mixture of Fe (0.84 g, 15 mmol), S_8 (0.48 g, 1.9 mmol), I_2 (1.27 g, 5 mmol) and Et_4NI (1.29 g, 5 mmol) in 100 mL tetrahydrofuran is heated under reflux for 24 h. The black solution is filtered hot, the solvent completely removed, and the residue dissolved in 250 mL dichloromethane. Crystallization, which commences after a few hours, is complete after three to four days at room temperature. 1.9 g (50%) of $(Et_4N)_2Fe_6S_6I_6$ is obtained. The platelet-shaped, black crystals can be stored for several days in the air.

[4] The $Ag_4M_2S_6$ groups (M = Mo, W) in the compounds $(R_3P)_4Ag_4M_2S_8$ have a structure similar to the Fe_6S_6 unit: A. Müller, E. Diemann, R. Jostes, H. Bögge, *Angew. Chem. 93* (1981) 957; *Angew. Chem. Int. Ed. Engl. 20* (1981) 934, and references cited therein; J. K. Stalick, A. R. Siedle, A. D. Mighell, C. R. Hubbard, *J. Am. Chem. Soc. 101* (1979) 2908.

[5] Cf. M. A. Bobrik, K. O. Hodgson, R. H. Holm, *Inorg. Chem. 16* (1977) 1851.

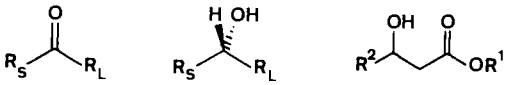
[6] G. B. Wong, M. A. Bobrik, R. H. Holm, *Inorg. Chem. 17* (1978) 578.

[7] S. Pohl, W. Saak, unpublished.

Preparative Microbial Reduction of β-Oxoesters with *Thermoanaerobium brockii*

By *Dieter Seebach**, *Max F. Züger*, *Fabio Giovannini*, *Bernhard Sonnleitner*, and *Armin Fiechter*

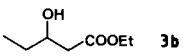
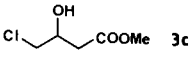
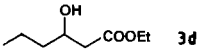
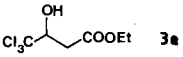
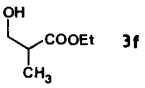
The usefulness of chiral, non-racemic starting materials for organic synthesis is increased if both enantiomers are available[1]. The microorganism most frequently used for enantioselective reductions of carbonyl compounds is baker's yeast *(Saccharomyces cerevisiae)*[2]. As with most other microorganisms and isolated enzymes, the hydrogen transfer follows *Prelog*'s rule[3] (see **1** → **2**). Reduction of β-oxoesters[4] produces 3-hydroxycarboxylic acid derivatives **3**, which are especially useful building blocks for syntheses. Depending upon the relative size of the groups R^1 and R^2 in the oxoester substrate, reduction may occur either from the *Re*- or from the *Si*-face[4,5] (see the third column of Table 1).



1 **2** **3**

R_S = smaller, R_L = larger substituent

Table 1. Comparison of the reductions of β-oxoesters and of 2-formylpropionate with baker's yeast (at 30°C) and with the thermophilic bacteria (at 72°C). The specific rotations were measured in $CHCl_3$ (*c* ca. 1.5).

Substrate	Reduction Product		Absol. Config./$[\alpha]_D$/%*ee* [Ref.] Yeast	*Th. brockii*
ethyl 3-oxobutanoate		**3a**	*S*/+41/97 [4]	*S*/+35/80
ethyl 3-oxopentanoate		**3b**	*R*/−13/40 [4]	*S*/+28/84
methyl 4-chloro-3-oxobutanoate		**3c**	*S*/−8/36 [11]	*R*/+21/89
ethyl 3-oxohexanoate		**3d**	*R*/−21/>90 [4]	*S*/+6/25
ethyl 4,4,4-trichloro-4-oxobutanoate		**3e**	*R*/−21/94 [12]	
ethyl 2-formylpropanoate		**3f**	*R*/−13/60 [13]	*R*/−16/72

We now report on the use of thermophilic bacteria[6], which are considered to be especially attractive for practical applications[7], to reduce β-oxoesters—sometimes with reversal of the stereochemical course of the reaction relative to that with yeast[8]. The reductions were carried out in a strictly anaerobic, continuously operated bioreactor of 3 L working volume with a culture of *Thermoanaerobium brockii (Th. brockii)*[9] growing in a TYEG medium (tryptone, yeast extract, glucose) containing sodium sulfide[10]. Charges of 20–100 mmol of the β-oxoesters listed in the

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first column of Table 1 were added all at once to the bioreactor. The first 10 L of solution withdrawn from the reactor was filtered, extracted with ethyl acetate, the organic solution dried ($MgSO_4$), the solvent evaporated, and the residue distilled in vacuo. In this way, the hydroxy esters **3** were isolated in yields ranging from 50 to 80%, with the enantiomeric excesses shown in the fourth column of Table 1.

As is evident from a comparison of the last two columns of Table 1, the yet more elaborate reduction by *Th. brockii* may lead to higher enantiomeric excesses than the yeast reduction. For both microorganisms, there are clearly substrates whose enantiotopic faces are poorly differentiated. Thus, the low (*S*)-selectivity of yeast reduction of methyl chloroacetoacetate becomes a high (*R*)-selectivity with the thermophilic bacteria. On the other hand, the hydride transfer by yeast to ethyl acetoacetate and ethyl trichloroacetoacetate occurs in the *same sense*[14]—in spite of the appreciable change of size of the R^2 (see **1**—**3**). The two halogenated β-hydroxy esters (*R*)-**3c** and (*R*)-**3e**, now available in high enantiomeric purity by microbial methods, are valuable starting materials for the synthesis of (*R*)-carnitin[5] and of (*R*)-malic acid[12].

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CAS Registry numbers:
(*S*)-**3** (R^1=Et, R^2=Me), 56816-01-4; (*S*)-**3** (R^1=Et, R^2=Et), 73143-67-6; (*R*)-**3** (R^1=Me, R^2=CH_2Cl), 88496-70-2; (*S*)-**3** (R^1=Et, R^2=Pr), 88496-71-3; ethyl 2-formylpropionate, 27772-62-9; ethyl (*R*)-3-hydroxy-2-methylpropionate, 87884-36-4; ethyl 3-oxobutanoate, 141-97-9; ethyl 3-oxovalerate, 4949-44-4; methyl 4-chloro-3-oxobutanoate, 32807-28-6; ethyl 3-oxohexanoate, 3249-68-1

[1] D. Seebach, E. Hungerbühler in R. Scheffold: *Modern Synthetic Methods 1980*, Salle + Sauerländer, Aarau 1980, p. 91; D. Seebach, M. F. Züger, *Helv. Chim. Acta 65* (1982) 495.
[2] A. Fischli in [1], p. 269.
[3] V. Prelog, *Pure Appl. Chem. 9* (1964) 119.
[4] R. U. Lemieux, J. Giguere, *Can. J. Chem. 29* (1951) 678; B. Seuring, D. Seebach, *Helv. Chim. Acta 60* (1977) 1175; G. Fráter, *Helv. Chim. Acta 62* (1979) 2825, 2829; B. Wipf, E. Kupfer, R. Bertazzi, H. G. Leuenberger, *Helv. Chim. Acta 66* (1983) 485; M. Hirama, M. Shimizu, M. Iwashita, *J. Chem. Soc. Chem. Commun. 1983*, 599.
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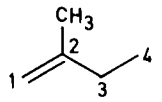
[7] Reviews: H. Zuber, *Chem. Unserer Zeit 13* (1979) 165; J. G. Zeikus, T. K. Ng, *Annu. Rep. Ferment. Processes 5* (1982) 263; B. Sonnleitner, A. Fiechter, *Trends Biotechnol. 1* (1983) 74.
[8] a) Zeikus et al. [8b] found that 2-pentanone is reduced by isolated alcohol dehydrogenase from *Thermoanaerobium brockii* to give (*R*)-2-pentanol (up to 80% *ee*), while Mosher et al. [8c] showed that fermenting yeast generates mainly the (*S*)-enantiomer (up to 64% *ee*); cf. also [10]. b) R. J. Lamed, E. Keinan, J. G. Zeikus, *Enzyme Microb. Technol. 3* (1981) 144; c) R. MacLeod, H. Prosser, L. Fikentscher, J. Lanyi, H. S. Mosher, *Biochemistry 3* (1964) 838.
[9] German collection of microorganisms, Göttingen (DSM No. 1457).
[10] Cf. J. G. Zeikus, P. W. Hegge, M. A. Anderson, *Arch. Microbiol. 122* (1979) 41.—Stirring rate 1000 rpm, pH 6.9, T=72°C, specific flow rate 0.3—0.5 h^{-1}, 30 L/h. N_2—Under these conditions, 2-pentanone is reduced to racemic 2-pentanol, cf. [8].—A detailed description of the biotechnological aspects of this work will be published separately: A. Fiechter et al., *Eur. J. Appl. Microbiol. Biotechnol.*, in press.
[11] Ratio of enantiomers determined using the method described by J. A. Dale, H. S. Mosher, *J. Am. Chem. Soc. 95* (1973) 512, by 300 MHz ^{1}H-NMR spectroscopy, cf. also [5].
[12] M. F. Züger, D. Seebach, *Helv. Chim. Acta 66* (1983) in preparation; % *ee* by hydrolysis to 4,4,4-trichloro-3-hydroxybutanoic acid and comparison of the specific rotation with that reported by H. Wynberg, E. G. J. Staring, *J. Am. Chem. Soc. 104* (1982) 166.
[13] M. F. Züger, F. Giovannini, D. Seebach, *Angew. Chem. 95* (1983) 1024; *Angew. Chem. Int. Ed. Engl. 22* (1983) 1012.
[14] Because of change of CIP-priority, the sense of chirality is specified opposite in the two cases.

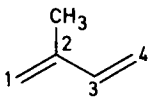
^{13}C-NMR INADEQUATE Spectrum with Broad Band Decoupling by Supercycles

By *Peter Bolte, Martin Klessinger**, and *Konrad Wilhelm*

The INADEQUATE pulse sequence[1] provides access even to small ^{13}C-^{13}C coupling constants in samples of natural abundance, but the experimental possibilities are often considerably limited by large line widths and poor suppression of the main signal. Herein we demonstrate with the spectra of 2-methyl-1-butene **1** and 2-methyl-1,3-butadiene **2** that these difficulties can be circumvented even in routine applications by a combination of the INADEQUATE method with an effective pulse sequence for proton decoupling[2].



1



2

Of the pulse sequences ("supercycles") for proton decoupling MLEV-64, WALTZ-16 and "R7"[3] tested by us, "R7" proved to be most effective for the investigations described here[4]. A comparison of INADEQUATE spectra with broad-band noise decoupling and with "R7" proton decoupling is provided in Figures 1a and b. Since simultaneous computer control of decoupler sequence and double quantum pulse program is not always simple, an external "black-box" decoupler control was developed[5]. To achieve a best possible suppression of the uncoupled ^{13}C-signal the sequence of 128 phase commands given by *Bax*[1] was employed. In the INADEQUATE spectrum of **1** shown in Figure 1b the uncoupled signal of C-3 is almost completely suppressed; the half-width of the lines is 0.25 Hz (corresponding to a line width of 0.12 Hz for one quantum transitions[1]). In addition to the coupling $^1J_{3,4}$=34.6 Hz, the two possible geminal couplings $^2J_{1,3}$=2.6 Hz and $^2J_{3,5}$=4.2 Hz are observable. All the NMR spectra discussed here were recorded with an evolution time τ=0.05 s; according to the relationship $I \sim \sin(2\pi J\tau)$ for the intensity of the doublet components, the coupling $^1J_{2,3}$=41.2 Hz falls in an intensity minimum and is therefore not observable in Figure 1.

The dependence of the signal intensity on the value of the coupling constants and the evolution time τ serves as an important aid for analysis of the spectra. Figure 1c shows the spectrum for C-4 of **1**. Once again, two pairs of signals are observable in addition to the ^1J-coupling with C-3. The two outer signals correspond to the doublet components of the coupling $^3J_{1,4}$=3.4 Hz; according to the expression given above the inner signal pair must, however, on the basis of the intensity, arise from two couplings, namely those of $^2J_{2,4}$=2.3 Hz and $^3J_{4,5}$=2.1 Hz, each of which could be resolved at the coupled nucleus.

All the coupling constants of **1** and **2** are collected in Table 1. Figure 2 illustrates to what degree these coupling constants could still be resolved and individually determined in our experiments. It was possible by extreme Gauss multiplication of the FID, in combination with a

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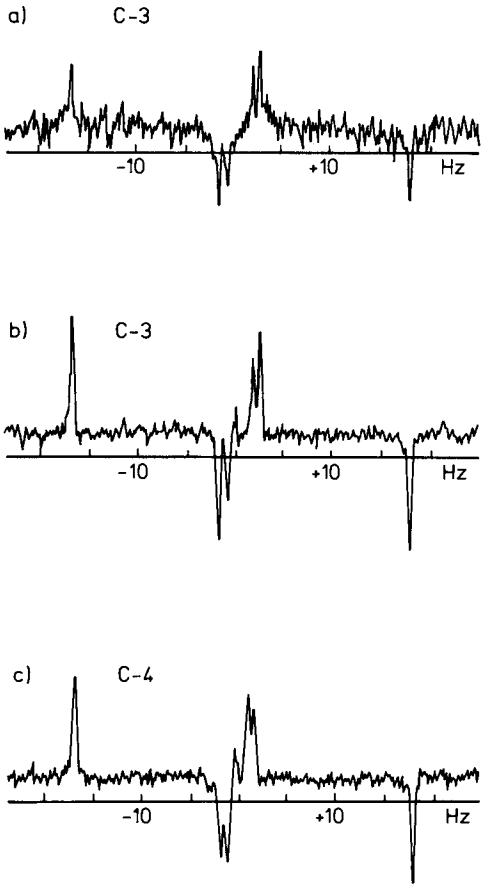

Fig. 1. INADEQUATE spectrum of the butene derivative **1** at 75 MHz (Bruker WM-300): a) with broad-band noise decoupling, b) and c) with "R7" proton decoupling. 1920 scans of 30 s each, τ adjusted to $J_{CC} = 5$ Hz, 80% solution in C_6D_6, 5-mm sample tube, 1 W decoupling power, point resolution 0.06 Hz/pt.

"power spectrum"[6], to resolve the three indirect couplings at C-1 in **1**. This is achievable with broad-band decoupling only with considerably higher decoupling power, whereupon inhomogenous heating of the sample can then lead to a splitting or broadening of the lines.

Table 1. ^{13}C-^{13}C coupling constants [Hz] of the hydrocarbons **1** and **2** [a].

Molecule	$J_{1,2}$	$J_{1,3}$	$J_{1,4}$	$J_{1,5}$	$J_{2,3}$	$J_{2,4}$	$J_{2,5}$	$J_{3,4}$	$J_{3,5}$	$J_{4,5}$
1	72.5	2.6	3.4	2.1	41.2	2.3	41.9	34.6	4.2	2.1
2	71.2	2.7	7.7	2.2	52.0	1.4	42.9	69.2	2.8	2.8

[a] The ^1J couplings were partly determined by conventional measurements.

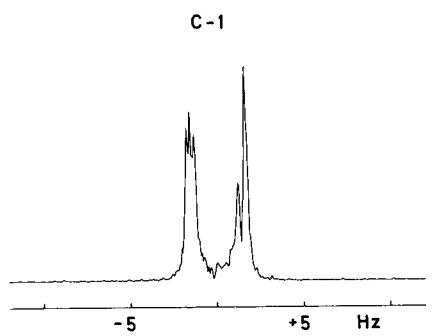

Fig. 2. INADEQUATE spectrum of **1** at 75 MHz. Conditions of measurement as in the case of Figure 1. Gauss multiplication of the FID with the exponents 0.1 and -0.001 and calculation of the "power spectrum".

Combination of the INADEQUATE pulse sequence with an effective broad-band decoupling sequence provides an effective method for the rapid determination of ^{13}C-coupling constants. This combination should thus also extend the possibilities of structural elucidation with INADEQUATE according to *Buddrus et al.*[7], as well as conformation analysis.

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CAS Registry numbers:
1, 563-46-2; **2**, 78-79-5

[1] A. Bax, R. Freeman, S. P. Kempsell, *J. Am. Chem. Soc. 102* (1980) 4849; A. Bax: *Two-Dimensional Nuclear Magnetic Resonance in Liquids*, Delft University Press, Delft 1982.
[2] A. J. Shaka, J. Keeler, R. Freeman, *J. Magn. Reson. 53* (1983) 313.
[3] A. J. Shaka, T. Frenkiel, R. Freeman, *J. Magn. Reson. 52* (1983) 159; J. S. Waugh, *ibid. 49* (1982) 517; A. J. Shaka, J. Keeler, T. Frenkiel, R. Freeman, *ibid. 52* (1983) 335.
[4] The efficacy of the various supercycles is strongly dependent on the errors in pulse length, phase and amplitude met with in practice [2, 5].
[5] R. Plettendorf, K. Wilhelm, unpublished.
[6] J. C. Lindon, A. G. Ferrige, *J. Magn. Reson. 44* (1981) 566.
[7] J. Buddrus, H. Bauer, H. Gotthardt, R. Jung, *Angew. Chem. 95* (1983) 565; *Angew. Chem. Int. Ed. Engl. 22* (1983) 548.

Cyclic Carboxylic Acid-Organoboron Compounds with BHB Bridge Bonding**

By *Peter Idelmann, Gerhard Müller, Walter R. Scheidt, Wilhelm Schüssler,* and *Roland Köster**

During investigations on the reduction of D-glucuronic acid with organoboranes $(R_2BH)_2$[1] IR spectroscopic measurements revealed the formation of some novel compounds, namely mixed associates of the unreduced acid with the diorgano-hydro-borane. Such associates are also formed even in solutions of simple monocarboxylic acids and can be preparatively isolated in crystalline form by choosing appropriately substituted educts.

When tetraorganodiboranes(6) $(R_2BH)_2$ [$R_2 = (C_2H_5)_2$, 1,5-C_8H_{14}] are mixed with double the amount of acyloxy(diorgano)boranes R_2BOCOR' [$R_2 = (C_2H_5)_2$, 1,5-C_8H_{14}; $R' = C_6H_{13}$, $C(CH_3)_3$, $CH{=}CHC_3H_7$, C_6H_5] in ether-free solutions at $\approx 20°C$, addition compounds are formed which show broad IR absorption bonds characteristic of a B–(μ-H)–B bond[2]. The mixed association already takes place at $\gtrsim 0°C$: a solution of 1 equivalent diethyl(pivaloyloxy)borane [1755 cm^{-1} ($\nu_{C=O}$); 1600 cm^{-1} ($\nu_{C=O\ldots B}$)] and 0.5 equivalents tetraethyldiborane(6) [1565 cm^{-1} (ν_{BH_2B})] in heptane, prepared at $-10°C$, affords on heating to $\approx 30°C$ the mixed associate [1980 cm^{-1} (ν_{BHB}); 1552, 1499 cm^{-1} ($\nu_{C\ldots OB}$, ring) in quantitative yield. Crystalline mixed associates **4a** and **4b** (melting and decomposition points $> 125-131°C$; temperature interval dependent on the rate of heating) can be prepared in almost quantitative yields from pivalic acid **1** or from 9-pivaloyloxy-9-

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[+] X-Ray structure analysis.

[++] DSC measurements.

[+++] IR spectroscopy.

[**] Boron Compounds, Part 58.—Part 57: M. Yalpani, R. Köster, *Chem. Ber. 116* (1983) 3332.

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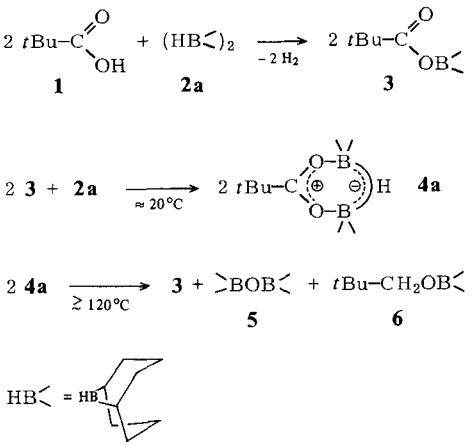
borabicyclo[3.3.1]nonane ("cyclooctane-1,5-diyl(pivaloyloxy)borane") **3** (m.p. = 99 °C) by reaction with bis(9-borabicyclo[3.3.1]nonane) **2a** or bis(9-deuterio-9-borabicyclo[3.3.1]nonane) **2b**, respectively, in heptane or in toluene.

In ethers, and especially in tetrahydrofuran, the species **4** are not stable at $\gtrsim 20$ °C. In hydrocarbons, the carboxylic acid is slowly reduced at $\gtrsim 30$ °C. Because of the formation of intramolecular oxygen-boron bonds, the aldehyde is formed quantitatively from the mixed associate of D-glucuronic acid and tetraethyldiborane(6)[1], whereas almost equimolar amounts of **3** and **6** are obtained from **4a** after cleavage of **5** both in solution as well as in the solid state.



According to the X-ray structure analysis[3] **4a** is made up of two crystallographically independent moieties. Each molecule has two organic bonded boron atoms, which form a six-membered ring with an OCO bridge through a 3c2e BHB bond (Fig. 1). The almost planar COBHBO ring of **4a** corresponds to the planar COBOBO ring in a conformer of the mixed associates of acyloxy-difluoro-boranes and alkoxy-difluoro-boranes[5].

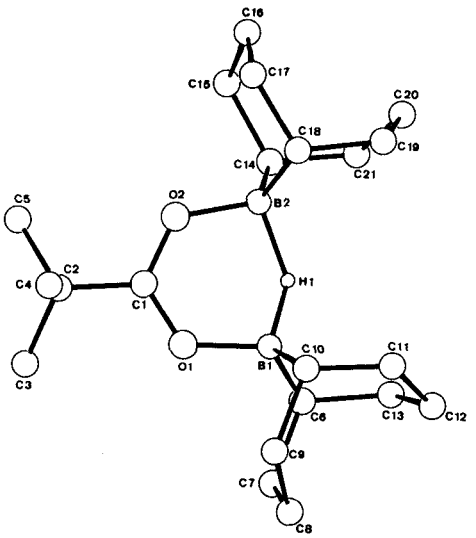


Fig. 1. Structure of **4a** in the crystal (molecule 1) [3, 4].

As can be seen in Figure 2, **4a** forms a layer lattice of molecular units distorted perpendicular to the *ac* plane in the crystal.

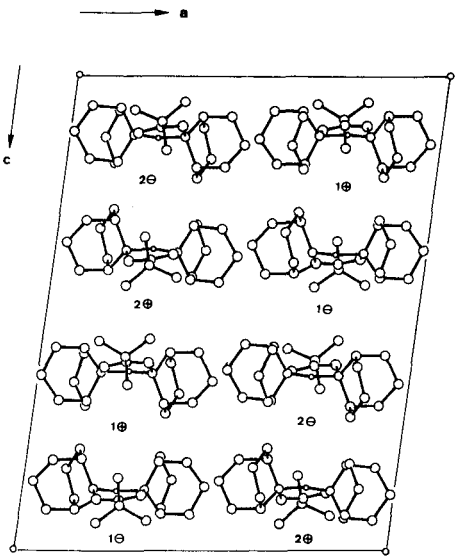


Fig. 2. Projection of the unit cell of **4a** on the *ac* plane. 1 and 2 are crystallographically independent molecules; ⊕ and ⊖ indicate their relative position perpendicular to the plane of projection.

In the solid state, **4a** and **4b** absorb heat at ≈ 80 °C and ≈ 77 °C, respectively (phase transformation), then dissipate heat (reaction) above ≈ 80 °C and ≈ 100 °C, respectively, and finally absorb heat (melting). In the case of **4b** the phase change is completely reversible, whereas in the case of **4a** it is only partially reversible (DSC measurements), because of the reaction that sets in during the phase transformation. The phase change in **4** presumably leads to reorientation of the molecules; this could explain the formation of the products **3**, **5**, and **6** on heating **4** to $\gtrsim 120$ °C.

Procedure

4a: A solution of **2a** (2.4303 g, 10.04 mmol) in heptane (6 mL) is treated with 1.025 g (10.04 mmol) **1** and the mixture stirred at ≈ 20 °C for ca. 19 h. Hydrogen (9.8 mmol, 97%) is slowly evolved. The volatile components are then removed from the white slurry under vacuum (10^{-3} torr) at $\lesssim 20$ °C. **4a** is obtained in 99% yield (3.41 g); from heptane, m.p. = 127–131 °C (decomp.).—MS[6a] (70 eV): *m/z* 344 (M^+), 222, 57 (100%).—^{1}H-NMR[6b] (60 MHz), [D$_8$]toluene): $\delta = 1.97$ (m, 24H), 1.03 (m, 4H), 0.91 (m, 9H).—^{11}B-NMR[6c] ([D$_8$]toluene): $\delta = 18.8$.—^{13}C-NMR[6c] (C$_6$D$_6$): $\delta = 188.24$ (s, 1C), 38.83 (s, 1C), 32.88 and 32.58 (t, 8C), 26.23 (q, 3C), 24.95 and 24.65 (t, 4C), ≈ 23.77 and ≈ 23.66 (br, 4C).—IR (KBr): 1980 cm^{-1} (broad and structured, ν_{BHB}), 1552, 1499 cm^{-1} ($\nu_{C\cdots OB}$, ring)[7].

4b: from heptane, m.p. = 125–130 °C (decomp.).—IR (KBr): 1572 (ν_{BDB}), 1498 ($\nu_{C\cdots OB}$, ring)[7].

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German version: *Angew. Chem. 96* (1984) 145

[1] R. Köster, P. Idelmann, W. V. Dahlhoff, *Synthesis 1982*, 650.
[2] a) P. Binger, G. Benedikt, G. W. Rotermund, R. Köster, *Justus Liebigs Ann. Chem. 717* (1968) 21; b) Y. Matsui, R. C. Taylor, *J. Am. Chem. Soc. 90* (1968) 1363; c) H. C. Brown, A. Khuri, S. Krishnamurthy, *ibid. 99* (1977) 6237.
[3] **4a**: monoclinic, $P2_1/n$, $a = 18.167(1)$, $b = 10.0891(9)$, $c = 23.198(1)$ Å, $\beta = 97.637(4)°$, $V = 4214.32$ Å^3, $Z = 8$, $d_x = 1.085$ g/cm^3, $Cu_{K\alpha}$, 8759 independent reflections, $R = 0.087$ for 4050 observed ($I > 2.0\sigma(I)$) reflections and 460 parameters, $R = 0.016$ ($w = 1/\sigma^2(|F_o|)$). Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopolds-

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hafen, on quoting the depository number CSD 50624, the names of the authors, and full citation of the journal.

[4] The differences in the B–H bond lengths lie within the standard deviation (molecule 1: 1.23(4), 1.44(4) Å; molecule 2: 1.41(4), 1.28(4) Å). BHB angles: 139(3) and 137(3)°; B...B distance: 2.500(8) Å (mean value).—The comparatively high R values and large standard deviations arise from the poor quality of the crystals of **4a**.

[5] H. Binder, W. Matheis, H.-J. Deiseroth, Han Fu-Son, *Z. Naturforsch. B 38* (1983) 554.

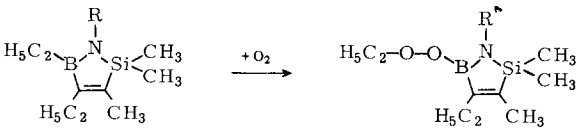
[6] Measurement: a) D. Henneberg, W. Schmöller; b) G. Schroth; c) R. Mynott, Max-Planck-Institut für Kohlenforschung.

[7] **4a** and **4b** had correct analyses (C, H, B, H^-).

Thermally Stable Ethylperoxyboron Unit by Regioselective Autoxidation**

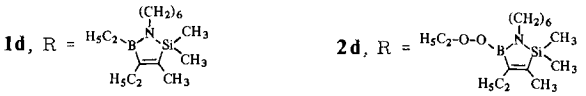
By *Roland Köster** and *Günter Seidel*

The surprisingly thermally stable ethylperoxyboron unit is formed by autoxidation of the heterocycles **1**. In heptane, **1a**—**c**[1] rapidly take up molecular oxygen at ca. 0—20 °C and form 4-ethyl-5-ethylperoxy-1-organo-2,2,3-trimethyl-2,5-dihydro-1*H*-1,2,5-azasilaboroles[***] **2a**—**c** highly regioselectively[2] (yields ≳80%). These can be purified without decomposition by vacuum distillation (see Table 1)[3]. The two heterocycle-containing compounds **1d** correspondingly react regioselectively with exactly **2** equivalents of O_2. Oily **2d** is isolated, and can be stored without decomposition at ≲ −20 °C.



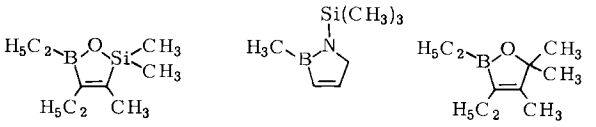
1 **2**

a, R = CH_3; **b**, R = C_6H_5; **c**, R = $CH_2C_6H_5$;



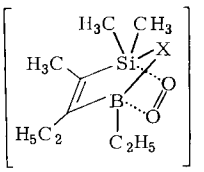
1d **2d**

The autoxidations, which proceed rapidly and afford pure ethylperoxyboron compounds, require the presence of certain atomic groupings in the unsaturated five-membered ring: pentaalkyl-2,5-dihydro-1,2,5-oxasilaboroles[***] such as **3**[4] rapidly take up 1 equivalent of O_2, even at −78 °C. Thermally stable compounds containing an ethylperoxyboron unit cannot however be isolated. In contrast 2-methyl-1-trimethylsilyl-2,5-dihydro-1*H*-1,2-azaborole[***] **4**[5], with an exocyclic trimethylsilyl group, does not react with molecular oxygen up to ≈100 °C. 2,3-Diethyl-4,5,5-trimethyl-2,5-dihydro-1,2-oxaborole[***] **5**[6], which contains the isopropylidene moiety in place of the dimethylsilanediyl group of **3**, is also completely stable towards oxygen up to ≈80 °C.



3 **4** **5**

We assume that the autoxidations of **1** and **3** proceed via oxygen associates **6** having [2.2.1]-structures.



6, X = NR, O

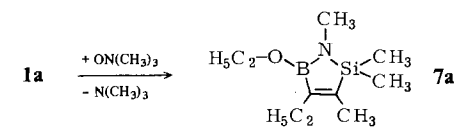
2a—**d** are stable at ≲ −20 °C in the liquid state. The undiluted compounds slowly turn dark brown at ≈20 °C. Presumably intermolecular redox reactions occur. An astonishing feature is the high thermal stability of **2a**—**c** in the gas phase[3]. This could be due to the fact that intermolecular reaction of the exocyclic ethylperoxy group with the BC_{vinyl} bond in the ring is sterically impossible.

2a—**d** are oxidizing agents. Triethylborane reacts with **2a** at ≈20 °C to give ethoxy(ethyl)boranes and 5-ethoxy-4-ethyl-1,2,2,3-tetramethyl-2,5-dihydro-1*H*-1,2,5-azasilaborole[***] **7a** (Table 1).

Table 1. Selected NMR data [7] of the compounds **1a**, **2a**, and **7a**.

	$\delta(^{11}B)$ ($\omega_{1/2}$ [Hz])	$\delta(^{13}C)$ C-5′	C-5″	$\delta(^{14}N)$	$\delta(^{17}O)$ O-5′	O-5″	$\delta(^{29}Si)$ $J(^{29}Si^{13}C)$ [Hz] C-2′	C-3
1a	44.8 (160)	6.8	8.1	−290	—	—	13.6 (76)	(52)
2a	30.0 (180)	71.5	13.2	−325	235.4	263.3	12.95 (73.2)	(53.7)
7a	29.6 (150)	60.1	18.3	−323	71	—	9.65 (75.1)	(53.7)

In analogy to the oxidation of the exocyclic BC bond of **1a**—**d** with oxygen, the oxidation of **1a** with an equimolar amount of trimethylamine *N*-oxide[8] in boiling toluene also proceeds uniformly. **7a** (b.p. = 27 °C/0.001 torr), which is stable to autoxidation, is formed in high yields[9].



1a **7a**

1a, however, is not oxidized by γ-picoline *N*-oxide[8] up to 110 °C. But reaction of the same reagent with **3** leads, exclusively via BC_{vinyl} oxidation, to high yields of 2,6-diethyl-4,4,5-trimethyl-4*H*-1,3,2-dioxasilaborinine[***] **8**. In contrast **3** reacts only slightly regioselectively with trimethylamine *N*-oxide, with formation of 70% **8** and 30% **9**.

The formation of the various O_2- and *N*-oxide products from the unsaturated five-membered rings **1** and **3** demonstrates that the atomic grouping around the acceptor atom

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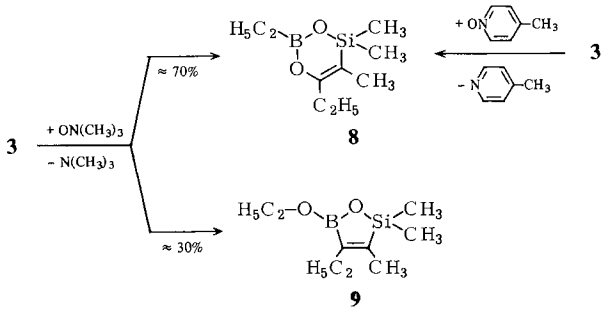
[**] Boron compounds, Part 59.—Part 58: P. Idelmann, G. Müller, W. R. Scheidt, W. Schüssler, K. Seevogel, R. Köster, *Angew. Chem. 96* (1984) 145; *Angew. Chem. Int. Ed. Engl. 23* (1984) 153.

[***] Concerning the nomenclature: The names of the heterocycles have been derived in accordance with the revised IUPAC Rules RB-1.2 to RB-1.4 (*Pure Appl. Chem. 55* (1983) 409). Names according to the previously valid rules: unsubstituted, **1**, **2**, **7**: Δ^3-1,2,5-azasilaboroline; **3**, **9**: Δ^3-1,2,5-oxasilaborolene; **4**: Δ^3-1,2-azaboroline; **5**: Δ^3-1,2-oxaborolene.



and the donor strength of the reagents decisively influence the regioselectivity of the oxidations.

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CAS Registry numbers:
1a, 79483-05-9; **1b**, 88636-23-1; **1c**, 88636-24-2; **1d**, 88636-25-3; **2a**, 88636-26-4; **2b**, 88636-27-5; **2c**, 88636-28-6; **2d**, 88636-29-7; **3**, 88636-30-0; **7a**, 88636-31-1; **8**, 88636-32-2; **9**, 88636-33-3;

[1] R. Köster, G. Seidel, *Angew. Chem. 93* (1981) 1009; *Angew. Chem. Int. Ed. Engl. 20* (1981) 972.

[2] a) Elemental analyses and spectroscopic data (cf. also Table 1) of the compounds **2a—d** and **7a** are consistent with the given structures.—b) **2a** (colorless liquid): ^{1}H-NMR (80 MHz, $CDCl_3$): $\delta = 4.08$ (q, $J = 7$ Hz, 2H), 2.70 (s, 3H), 2.06 (q, $J = 7.5$ Hz, 2H), 1.70 (s, 3H), 1.21 (t, $J = 7$ Hz, 3H), 0.85 (t, $J = 7.5$ Hz, 3H), 0.09 (s, 6H); MS: *m/z* 227 (30%, M^+), 212 (30), 152 (24), 114 (100), 59 (73).—c) **7a** (colorless liquid): ^{1}H-NMR (80 MHz, $CDCl_3$): $\delta = 4.18$ (q, $J = 7$ Hz, 2H), 2.60 (s, 3H), 2.19 (q, $J = 7.5$ Hz, 2H), 1.74 (s, 3H), 1.24 (t, $J = 7$ Hz, 3H), 0.90 (t, $J = 7.5$ Hz, 3H), 0.09 (s, 6H); MS: *m/z* 211 (45%, M^+), 196 (100), 152 (18), 114 (17), 59 (25), 29 (27).

[3] **2**: A solution of **1a** (3.5 g, 18 mmol) in heptane (10 mL) is treated at 0 to 20°C with pure oxygen in the complete absence of moisture. After 2 h a total of 392 mL (97%) of O_2 is taken up. The solution is concentrated at 14 torr (bath: ≤20°C) and colorless **2a** (3.8 g, 93%) is distilled off (b.p. = 30—34°C/0.011 torr; bath: ≤50°C). Liquid **2a** is stored at < −20°C; at > −10°C, redox reactions take place and the solution slowly darkens.—**2b**: 85%; b.p. = 80°C/0.001 torr; **2c**: 79%; b.p. = 40—50°C/0.001 torr.

[4] a) R. Köster, G. Seidel, unpublished, 1981.—b) Cf. also Houben-Weyl: *Handbuch der Organischen Chemie*, 4 edit., *Vol. XIII/3a*, Thieme, Stuttgart 1982, p. 600f.—c) See [4b]; *Vol. XIII/3b*, 1983, p. 553.—d) **1a** reacts quantitatively with water to give the methylamine adduct of **3**, from which pure **3** (b.p. = 70°C/14 torr) is obtained by reaction with $(C_2H_5)_2O{-}BF_3$.

[5] J. Schulze, R. Boese, G. Schmid, *Chem. Ber. 114* (1981) 1297; NMR-Spectra (^{1}H, ^{11}B) of **3**: G. Schmid, U. Höhner, D. Kampmann, *Z. Naturforsch. B38* (1983) 1094.

[6] a) R. Köster, G. Seidel, unpublished, 1976.—b) see [4b], *Vol. XIII/3a*, 1982, p. 568.—c) **5**, b.p. = 42°C/0.09 torr, is obtained in 68% yield on reaction of sodium (3-diethylboryloxy-3-methyl-1-butynyl)triethyl-borate with dimethyl sulfate.

[7] ^{13}C-, ^{14}N-, and ^{29}Si-NMR-data: Dr. B. Wrackmeyer, Universität München.—All the other NMR data: Dr. R. Benn, Max-Planck-Institut für Kohlenforschung, Mülheim a. d. Ruhr.

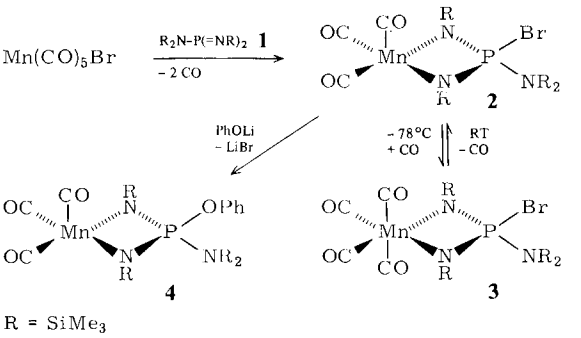
[8] R. Köster, Y. Morita, *Angew. Chem. 78* (1966) 589; *Angew. Chem. Int. Ed. Engl. 5* (1966) 580; *Justus Liebigs Ann. Chem. 704* (1967) 70.

[9] See [4b], *Vol. XIII/3b*, 1983, p. 195.

Synthesis and Structure of a Five-Coordinate Manganese(I) Complex**

By *Otto J. Scherer*, Jürgen Kerth,* and *William S. Sheldrick*

Coordination number six and 18-electron system are characteristic for manganese(I) compounds (d^6 complexes)[1]. Five-coordinate 16-electron manganese(I) complexes have hitherto only been detected IR spectroscopically in the matrix[2], and as short-lived, dynamic intermediates in kinetic studies[3]. According to theoretical studies[4], the preferred geometry for d^6 systems (ML_5) is the "flat" square pyramid. However, in the case of the recently characterized $ReCl(Ph_2PCH_2CH_2PPh_2)_2$[5] the crystal structure analysis revealed a trigonal-bipyramidal environment at the rhenium. We have now obtained the isolable five-coordinate manganese(I) complexes **2** and **4** from $Mn(CO)_5Br$ and the double ylide **1**.



R = $SiMe_3$

2 and **4**[6] form permanganate colored crystals, **3** forms yellow-brown crystals, each of which are readily soluble in ether, benzene, *n*-hexane, and dichloromethane. **2** already reacts with carbon monoxide at −78°C to give the tetracarbonyl complex **3** (18-electron system, **2** is regenerated at room temperature and weak vacuum), whereas **4** does not react with CO even at room temperature (normal pressure). In contrast to the extremely air-sensitive **2**, complex **4** can be handled in the open atmosphere for short periods.

In the ^{1}H-NMR spectra (200 MHz, CD_2Cl_2, TMS) a restriction to rotation about the P—NR_2 bond can be de-

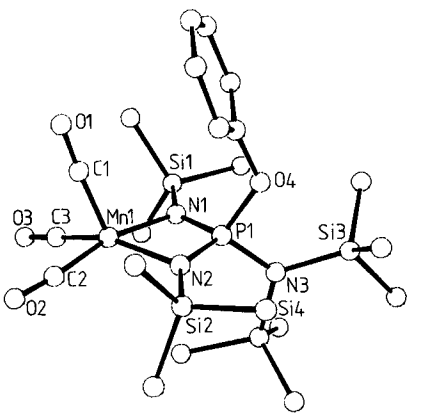


Fig. 1. Structure of **4** (molecule 1) in the crystal. Selected bond lengths [Å] and angles [°] (see also text): Mn1—N1 2.040(5), Mn1—N2 2.013(5), N1—Si1 1.692(5), N2—Si2 1.726(5), N3—Si3 1.805(6), N3—Si4 1.775(6), P1—N1 1.595(5), P1—N2 1.588(6), P1—N3 1.645(6), P1—O4 1.613(5); C1—Mn1—C2 89.1(4), C1—Mn1—C3 88.6(3), C2—Mn1—C3 84.4(4), N1—Mn1—N2 74.4(2), Mn1—N1—P1 91.7(3), Mn1—N2—P1 92.8(3), N1—P1—N2 100.7, O4—P1—N3 97.6(3); sum of angles at N1 360.1, N2 359.8, N3 359.9. Crystallographic data: space group monoclinic, $P2_1/c$; $a = 21.223(4)$, $b = 17.363(4)$, $c = 17.859(4)$ Å, $\beta = 98.63(2)°$; $Z = 8$, $\rho_{calc} = 1.22$ g cm^{-3}. 4207 independent reflections ($Mo_{K\alpha}$, $F_0^2 \geq 3.0\sigma(F_0^2)$, $2\theta \leq 45°$); $R = 0.068$, $R_w = 0.054$. Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD 50590, the names of the authors, and full citation of the journal.

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tected, at room temperature in the case of **4**, at −20°C in the case of **2** and **3**. The fluxional properties of **2** and **4** are visible in the $^{13}C\{^1H\}$-NMR spectrum (CD_2Cl_2, TMS int., 203 K). Even at −70°C only one CO singlet is observed for **2** ($\delta = 227.4$) and **4** ($\delta = 227.1$), whereas for **3** three singlets are observed (217.2 (2CO), 207.7 (1CO), 207.5 (1CO))[7].

In the case of **4** (two independent molecules with no significant difference in bond lengths and bond angles), the crystal structure analysis (Fig. 1, molecule 1) reveals a distorted square-pyramidal environment at the manganese. Whereas the $Mn(CO)_3$ moiety corresponds to the section of an undistorted octahedron, in the chelate moiety a marked widening of the angle is found between the apical CO group and the basal N atoms (C1–Mn1–N1 103.9(3), C1–Mn1–N2 114.2(3)°). In the case of square-pyramidal d^6-complexes, theory[4a] predicts a strengthening of the apical bond for an angle of < 165° between the oppositely situated basal atoms. Molecule 1 of **4** (Fig. 1) with an average value of *ca.* 162° (C2–Mn1–N1 166.7(3), C3–Mn1–N2 157.0(3)°) reveals this trend (Mn1–$C1_{ap}$ 1.748(8), Mn1–$C2_{ba}$ 1.777(9), Mn1–$C3_{ba}$ 1.786(8) Å), whereas molecule 2 does not (average value *ca.* 163°; Mn2–$C1_{ap}$ 1.775(8), Mn–$C2_{ba}$ 1.781(8), Mn2–$C3_{ba}$ 1.751(9) Å). Probably the two angles still lie too near to the limiting value of 165° (moreover, the influence of the twisted NPN chelate moiety is unknown). The Si–N_{ring} bond lengths (average value 1.71 Å) are markedly shorter[8] than the Si–N bond lengths in the P–$N(SiMe_3)_2$ group (average value 1.79 Å). The four-membered ring and the environment of the N atoms are planar. **4** is diamagnetic (susceptibility measurement).

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[1] See e.g. F. A. Cotton, G. Wilkinson: *Advanced Inorganic Chemistry*, 4th Ed., Wiley-Interscience, New York 1980, p. 736; P. M. Treichel in G. Wilkinson, F. G. A. Stone, E. W. Abel: *Comprehensive Organometallic Chemistry*, Vol. 4, Pergamon Press, Oxford 1982, p. 1.

[2] T. M. McHugh, A. J. Rest, D. J. Taylor, *J. Chem. Soc. Dalton Trans. 1980*, 1803.

[3] J. D. Atwood, T. L. Brown, *J. Am. Chem. Soc. 97* (1975) 3380; *98* (1976) 3155, 3160.

[4] See e.g. a) A. R. Rossi, R. Hoffmann, *Inorg. Chem. 14* (1975) 365; b) M. Elian, R. Hoffmann, *ibid. 14* (1975) 1058; c) J. K. Burdett, *Inorg. Chem. 15* (1976) 212; d) D. A. Pensak, R. J. McKinney, *ibid. 18* (1979) 3407.

[5] D. L. Hughes, A. J. L. Pombeiro, C. J. Pickett, R. L. Richards, *J. Organomet. Chem. 248* (1983) C26.

[6] The structure of a $(OC)_4MnBr(RN)_2P(NR_2)$ originally quoted by us for **2** (O. J. Scherer, J. Kerth, B. K. Balbach, M. L. Ziegler, *Angew. Chem. 94* (1982) 149; *Angew. Chem. Int. Ed. Engl. 21* (1982) 136; *Angew. Chem. Suppl. 1982*, 169) must be corrected.—Procedure: **2**: A suspension of **1** (2.56 g, 7 mmol) (O. J. Scherer, N. Kuhn, *Chem. Ber. 107* (1974) 2123) and $Mn(CO)_5Br$ (1.92 g, 7 mmol) in anhydrous benzene (30 mL) is stirred for *ca.* 4 h at 50°C, the pressure being reduced every 20 min for *ca.* 2 min to *ca.* 0.01 bar. Termination of reaction can be determined IR and ^1H-NMR spectroscopically. After removal of the benzene in vacuo the residue is taken up in 17 mL anhydrous *n*-hexane, filtered over filter flocs (G3 frit), and slowly cooled within 5 d to −85°C. Crystalline **2** separates out (yield 2.6 g (61%)).—**4**: A suspension of **2** (500 mg, 0.86 mmol) and crude LiOPh (113.5 mg, 1.12 mmol; prepared from PhOH + *n*BuLi) in anhydrous *n*-hexane (10 mL) is stirred for 1 h at 50°C, cooled to 0°C, and filtered over filter flocs. After removal of solvent in vacuo the crude product is recrystallized from hot acetonitrile. Yield 365 mg (71%).

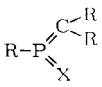
[7] $^{31}P\{^1H\}$-NMR (CD_2Cl_2, H_3PO_4 ext): $\delta = -1.9$ (s) (**2**), −13.6 (s) (**3**), 22.8 (s) (**4**).—IR (*n*-hexane): νCO: 2028 (s), 1938 (vs), 1935 (vs), 1904 (w) (**2**); 2085 (s), 2003 (vs), 1990 (vs), 1950 (vs), (**3**); 2028 (s), 1930 (vs), 1925 (vs), 1895 (w) (**4**).

[8] Cf. also W. Keim, R. Appel, A. Storeck, C. Krüger, R. Goddard, *Angew. Chem. 93* (1981) 91; *Angew. Chem. Int. Ed. Engl. 20* (1981) 116.

The First Stable Methyleneoxophosphorane**

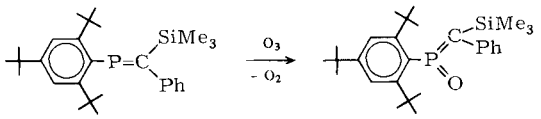
By *Rolf Appel**, *Falk Knoch*, and *Holger Kunze*

Numerous reports have appeared in recent years in which attempts to synthesize the methyleneoxo- and -thioxophosphoranes **1** are described[1,2]. With the exception of a methylenethioxophosphorane substituted at the P atom by a disilylamino group[3], all previous examples of this compound type are highly reactive, transient intermediates and detectable only via trapping reactions.



1a: X = O; **1b**: X = S

We have now found, however, that the phosphaethene **2**, bearing the very bulky 2,4,6-tri-*tert*-butylphenyl group at phosphorus[4], is specifically oxidized by ozone, even at −78°C, to afford the methyleneoxophosphorane **3**. The reaction was followed spectroscopically, since excess ozone leads to secondary reactions.



2 **3**

Colorless crystals of **3** were obtained from acetonitrile. Their composition was determined by elemental analysis and from the mass spectrum, and the structure (Fig. 1) established by X-ray structure analysis[5]. The NMR data[6] are consistent with structure **3**.

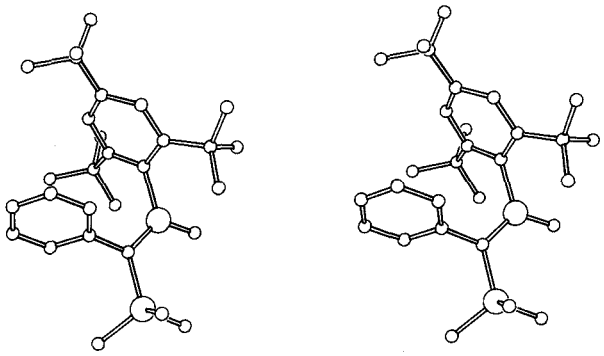


Fig. 1. Structure of **3** in the crystal [5]; stereoscopic projection (without H atoms).

3 slowly reacts with alcohols, the otherwise commonly trapping reagents for these species, to give phosphinic acid esters. The action of sulfur on solutions of **2** in triethylamine affords the corresponding methylenethioxophosphorane of type **1b**.

Procedure

A stream of O_2/O_3 from a commercially available ozone generator is bubbled into a solution of **2** (3.51 g, 8 mmol)

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[**] Low-Coordinated Phosphorus Compounds, Part 26. - Part 25: R. Appel, S. Korte, *Z. Anorg. Allg. Chem.*, in press.

in 50 mL toluene cooled with methanol/dry ice (monitored by ^{31}P-NMR) until the conversion is quantitative. After the solution has been allowed to warm up to room temperature, the solvent is removed in vacuo, the residue taken up in a little acetonitrile, and the spontaneous crystallization completed in the refrigerator at ca. −2°C. Yield: 2.11 g (58%), m.p. = 93°C.

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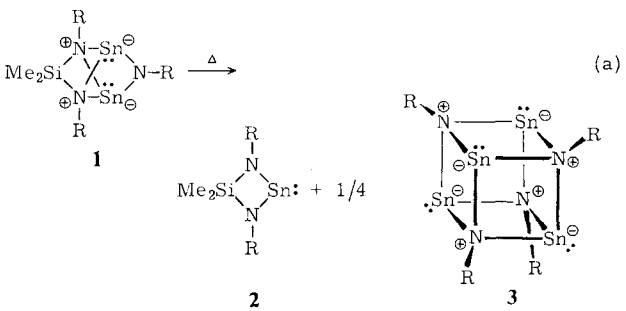
[1] M. Regitz, G. Maas, *Top. Curr. Chem. 97* (1981) 71.
[2] T. A. van der Knaap, T. C. Klebach, R. Lourens, M. Vos, F. Bickelhaupt, *J. Am. Chem. Soc. 105* (1983) 4026.
[3] E. Niecke, D. A. Wildbredt, *J. Chem. Soc. Chem. Commun. 1981*, 72.
[4] R. Appel, U. Kündgen, unpublished.
[5] Molecular structure of **3**: triclinic, $P\bar{1}$, $a = 921.1(4)$, $b = 1046.0(4)$, $c = 1536.4(11)$ pm, $\alpha = 76.24(4)$, $\beta = 83.09(5)$, $\gamma = 86.38(3)°$, $V = 1426.4 \times 10^6$ pm^3, $\rho_{calc.} = 1.06$ g/cm^3, $Z = 2$. The structure was determined by direct methods (SHELXTL) from 3731 single crystal diffractometer data and refined to $R = 6.8\%$ ($R_w = 5.5\%$) Geometry: sum of angles at P = 359.7° (almost planar), angle between the aryl plane and the POC plane 80°; angles $C_{aryl}PO$ 121.0, $C_{aryl}PC$ 113.1, POC 125.6°; distances P=O 145.8(3), P=C 165.7(4), O···C 277 pm (aryl = 2,4,6-tri-*tert*-butylphenyl). Further details on the crystal structure investigation can be obtained from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen by quoting the depository number CSD 50591, the names of the authors, and the journal citation.
[6] Selected NMR parameters: ^{31}P{^{1}H}-NMR (C_6D_6, 32.2 MHz, H_3PO_4 ext.): $\delta = 153.7$ (s); ^{13}C{^{1}H}-NMR (C_6D_6, 20.0 MHz, TMS int.): $\delta = 103.8$ (d), $J(P{=}C) = 113.2$ Hz.

$Sn_3(NtBu)_2(OtBu)_2$, A Molecule with a Novel, Heptaatomic, Polycyclic Framework**

By *Michael Veith** and *Walter Frank*

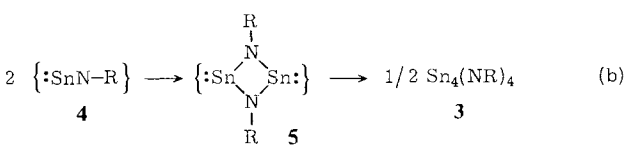
When strongly heated, the tricyclic compound **1** is quantitatively converted into **2** and **3** (R = *t*Bu)[1].



(a)

1 **2** **3**

The rate-determining step of this reaction follows a first order rate law[1]. We therefore assumed that *tert*-butyliminostannanediyl ("-stannylene") is initially formed as an unstable intermediate, from which the stable tetramer **3** is formed stepwise[2].



(b)

4 **5** **3**

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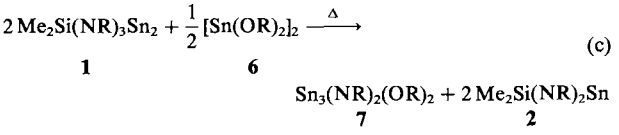
[**] Cyclic Diazastannylenes, Part 20. This work was supported by the Fonds der Chemischen Industrie.—Part 19: M. Veith, M. Grosser, V. Huch, *Z. Anorg. Allg. Chem.*, in press.

To establish the mechanism of reaction we have now repeated the thermolysis of **1** in the presence of a potential trapping reagent for **4** or **5**; we chose for this purpose the dimeric tin(II) bis(*tert*-butoxide) **6**[3], which is loosely bound in solution, for it proved useful in the "trapping" of monomeric thallium(I) *tert*-butoxide with formation of $Tl(OtBu)_3Sn$[4].



(c)

1 **6** **7** **2**

The novel compound **7**[5], which is still stable even above 250°C, is also formed with a twentyfold excess of **6**. Its composition is confirmed by elemental analysis, mass spectrum and ^{1}H-NMR spectrum. As the X-ray structure analysis shows, the molecule **7** has a crystallographic plane of symmetry (cf. Figure 1); the deviation from the higher point symmetry C_{2v} (mm2) is however insignificant, so this symmetry can be assigned to the free molecule. Supporting evidence for this is provided by the ^{1}H-NMR spectrum of **7** [in toluene, $\delta = 1.28$ (s, 18 H) and 1.58 (s, 18 H)], which indicates the same chemical environment for each of the pairs of *tert*-butyl groups at the nitrogen and oxygen atoms independently of the temperature (−80 to +40°C). Purely geometrically, the heptaatomic cyclic moiety in **7**, which to our knowledge is a novelty in the structural chemistry of cage-like polycycles, can be regarded as made up of two trigonal bipyramids (SnN_2OSn) with a common face (SnN_2). Four of the seven atoms forming the "cage" bear *tert*-butyl substituents, which are oriented in the direction of the apices of a distorted bisphenoid.

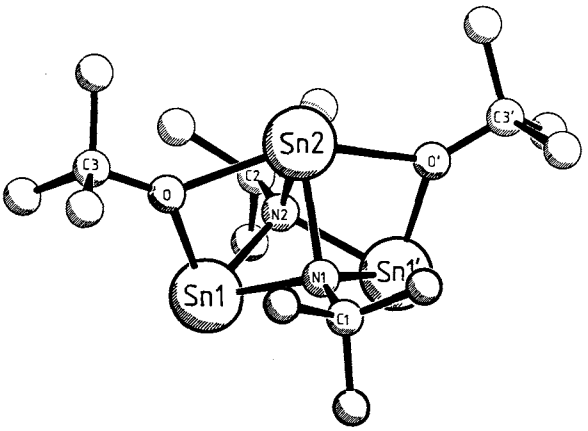


Fig. 1. Molecular structure of **7** in the crystal (orthorhombic, space group Cmca, $a = 1758.6(9)$, $b = 1236.7(9)$, $c = 2192(1)$ pm, $Z = 8$, $\rho_{exp} = 1.81$ g cm^{-3}; 1380 independent reflections/115 parameters, $R = 0.054$). Further details of the crystal structure investigation are available from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen, on quoting the depository number CSD 50653, the names of the authors, and full citation of the journal.

Table 1. Selected bond lengths [pm] and angles [°] in the molecule **7**.

Sn1–O	210.0(5)	O–Sn1–N1	83.4(3)	Sn1–O–Sn2	88.0(2)
Sn1–N1	219.7(6)	O–Sn1–N2	83.4(3)	Sn1–O–C3	135.4(5)
Sn1–N2	219.8(5)	N1–Sn1–N2	68.4(2)	Sn2–O–C3	136.6(5)
Sn2–O	237.4(6)	O–Sn2–O′	147.9(3)	Sn1–N1–Sn2	88.7(3)
Sn2–N1	225.8(9)	O–Sn2–N1	76.2(1)	Sn1–N1–Sn1′	96.2(2)
Sn2–N2	220.1(8)	O–Sn2–N2	77.3(1)	Sn1–N1–C1	123.5(4)
O–C3	142(1)	N1–Sn2–N2	67.3(3)	Sn2–N1–C1	126.3(7)
N1–C1	149(2)			Sn1–N2–Sn2	90.2(2)
N2–C2	154(1)			Sn1–N2–Sn1′	96.2(2)
				Sn1–N2–C2	122.2(3)
				Sn2–N2–C2	127.0(6)

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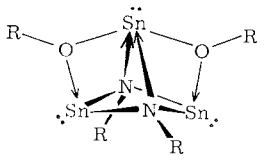
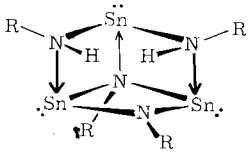
Two of the three tin atoms in **7** are trigonal-pyramidally coordinated, whereas one (Sn2) has four nearest neighbors. Thus, the usual coordination number 3 for Sn^{II} atoms is not only overstepped in larger molecular cages[6] but also in strongly strained systems. The environment at the nitrogen atom is distorted-tetrahedral, that at the oxygen atom trigonal planar. In the chemical formulation of **7** the bonding may simply be described with donor acceptor bonds symbolized by arrows.



7



8

This description of the structure is not only formal (cf. Table 1). The molecule **7** is therefore to be regarded as a Lewis acid-base adduct of **5** and monomeric **6**. Control experiments and kinetic investigations suggest that **5** occurs as intermediate in reaction (a): Thus, e.g., no reaction takes place between **3** and **6**, even under extreme conditions (sealed tube, 270°C).

Other heptaatomic polycycles are known, but their structures mostly derive from the "open" norsecocubane[7]. An example of this type of structure is $Sn(NR)_2(NHR)_2$ **8**[8]. On comparing **8** and **7** there is a very striking similarity in composition, and in a broad sense (replacement of NH by O) they are even isosteric. The sp^3 hybridization brought about in **8** by the hydrogen atoms on the nitrogen atoms leads to the norsecocubane-like structure, whereas in **7** the oxygen atoms are sp^2 hybridized and thus facilitate the formation of the "closed" polycycle.

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CAS Registry numbers:
1, 71262-29-8; **6**, 84913-53-1; **7**, 88589-48-4.

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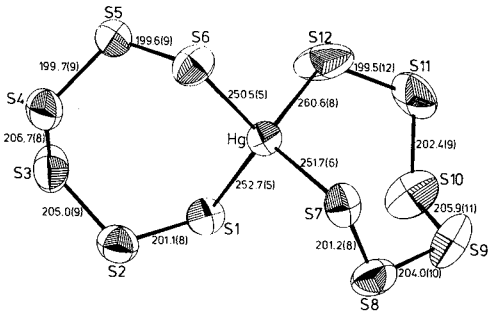
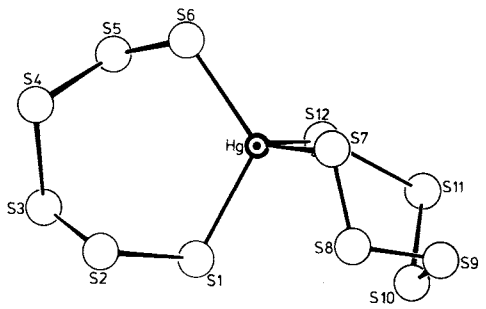
[2] M. Veith, O. Recktenwald, *Top. Curr. Chem. 104* (1982) 1.
[3] M. Veith, F. Töllner, *J. Organomet. Chem. 246* (1983) 219.
[4] M. Veith, R. Rösler, *Angew. Chem. 94* (1982) 867; *Angew. Chem. Int. Ed. Engl. 21* (1982) 858.
[5] A mixture of **1** (3.14 g, 6.2 mmol) and **6** (0.82 g, 1.55 mmol) is heated without solvent for 30 min at 210°C. **2** is isolated from the solid reaction mixture by condensation (spectroscopic characterization [2]) at 40°C/0.01 torr, while **7** is obtained by sublimation at 80°C/0.001 torr. Recrystallization from toluene furnishes 1.78 g (89%) colorless **7** (m.p. 129°C), which is readily soluble in benzene, hexane, and diethyl ether.
[6] P. G. Harrison, B. J. Haylett, T. J. King, *J. Chem. Soc. Chem. Commun. 1978*, 112.
[7] H. Nöth, P. Wolfgardt, *Z. Naturforsch. B31* (1976) 697.
[8] M. Veith, *Z. Naturforsch. B35* (1980) 20.

Isolation of a Sulfur-Rich Binary Mercury Species from a Sulfide-Containing Solution: $[Hg(S_6)_2]^{2\ominus}$, a Complex with $S_6^{2\ominus}$ Ligands

By *Achim Müller**, *Jürgen Schimanski*, and *Uwe Schimanski*

The increased solubility of heavy metal sulfides of the "H_2S group" of the analytical separation procedure of the cations (e.g. of HgS) in alkaline sulfide-containing solutions is not only of general chemical interest (possible formation of unusual thiometalates[1,2]) but also of analytical and mineralogical interest[3–5]. Sulfide mineral ores are mainly formed hydrothermally (from post-magmatic fluids); it appears remarkable that the formation of many ore deposits cannot be conclusively explained because of the very small solubility products (e.g. of α-HgS, cinnabar)[3–5]. We have been able to demonstrate that definite novel complexes of metals such as Cu, Ag, Au, and Hg are





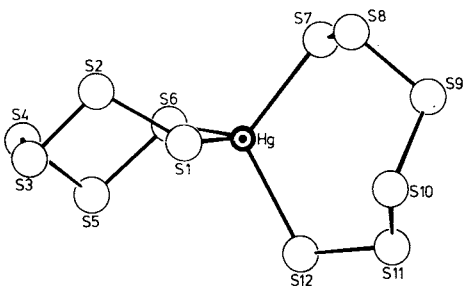


Fig. 1. Structure of the anionic complex **1a** (three projections) in the crystal of the tetraethylammonium salt **1** [space group $P2_1/c$, $a = 1283.1(5)$, $b = 1762.9(7)$, $c = 1455.6(5)$ pm, $\beta = 97.42(3)°$, $Z = 4$; Syntex $P2_1$, $Mo_{K\alpha}$, $R = 0.086$ for 3593 independent reflections ($F_0 > 3.92\sigma(F_0)$)]. Bond angles: S1–Hg–S6 117.0(2), S1–Hg–S7 109.2(2), S1–Hg–S12 99.6(2), S6–Hg–S7 109.6(2), S6–Hg–S12 107.4(2), S7–Hg–S12 113.9(2), Hg–S–S (mean value) 108.4, S–S–S (mean value) 108.6°. Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen, on quoting the depository number CSD 50593, the names of the authors, and full citation of the journal.

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formed in polysulfidic solutions which may be of significance in this connection.

Reaction of mercury(II) acetate with methanolic polysulfide solution in the presence of tetraethylammonium iodide leads to formation of orange-colored $(Et_4N)_2[Hg(S_6)_2]$ **1**[6]. In the anionic complex $[Hg(S_6)_2]^{2\ominus}$ **1a**, the first homoleptic complex with bidentate $S_6^{2\ominus}$ ligands, the central Hg atom is surrounded by a distorted tetrahedral array of S atoms (Fig. 1)[8]. The mean Hg–S distance is—as expected—very similar to that in β-HgS with the zinc blende structure (253 pm)[2].

The two $S_6^{2\ominus}$ units in **1a** have a similar conformation, whereas the two HgS_6 heterocycles have a different structure (cf. the three projections in Fig. 1). The coordinating (S1, S6 and S7, S12) as well as the next but one S atoms (S3, S4 and S9, S10) of the hexasulfido ligands each lie almost in a plane; the remaining S atoms (S2,S5 and S8,S11) lie approximately 100 pm above or below these planes. The Hg atom is located almost in the {S1, S3, S4, S6} "plane", but distinctly outside (105 pm) the {S7, S9, S10, S12} plane.

The compound **1** cannot be characterized very well by IR spectroscopy (moderately strong band at 495 and weak band at 485 cm^{-1}) because of the low polarity of all the bonds. However, the characteristic intense main bands at 460 and 196 cm^{-1} in the solid-state Raman spectrum ($\lambda_e = 647.1$ nm) may be used for its detection (assignment: totally symmetric ring breathing and deformation vibration, both practically localized in the $S_6^{2\ominus}$ ligand). The solid-state electronic spectrum (reflectance; dispersion on cellulose) shows a band at 350 nm with two slightly pronounced shoulders at 285 and 402 nm.

On the basis of our findings, it would appear possible that besides sulfido-[4,5] also polysulfidometalates participated in the formation of metal sulfide as for instance cinnabar deposits. The transport of "metals together with sulfur"[4] in the form of soluble polysulfido species could be explained principally in this way.

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CAS Registry number:
1, 88610-33-7

[1] The enhanced solubility of HgS in aqueous solutions of alkali metal sulfides is, according to a Raman spectroscopic investigation, probably due to the formation of the linear $[SHgS]^{2\ominus}$ anionic complex: R. P. J. Cooney, J. R. Hall, *Aust. J. Chem. 19* (1966) 2179.

[2] Cf. C. A. McAuliffe: *The Chemistry of Mercury*, MacMillan Press, London 1977.

[3] H. Schröcke, K. L. Weiner: *Mineralogie*, de Gruyter, Berlin 1981; H. J. Rösler: *Lehrbuch der Mineralogie*, VEB Deutscher Verlag für Grundstoffindustrie, Leipzig 1981.

[4] K. B. Krauskopf: *Introduction to Geochemistry, 2nd Ed.*, McGraw-Hill, New York 1979; *Naturwissenschaften 48* (1961) 441.

[5] G. Schwarzenbach, M. Widmer, *Helv. Chim. Acta 46* (1963) 2613.

[6] Et_4NI (4 g) is dissolved with stirring in a freshly prepared methanolic solution of ammonium polysulfide (50 mL) [7]. After addition of 0.75 g $Hg(CH_3COO)_2$ the mixture is heated briefly at 50°C (initially precipitated mercury sulfide almost completely redissolves), filtered, and the dark brown filtrate is stored in a closed vessel at 20–25°C (2–3 d). The orange crystals of **1** that precipitate out are washed with toluene; yield 1.2 g.

[7] Cf. A. Müller, E. Krickemeyer, H. Bögge, W. Clegg, G. M. Sheldrick, *Angew. Chem. 95* (1983) 1030; *Angew. Chem. Int. Ed. Engl. 22* (1983) 1006.

[8] M. Schmidt and G. Hoffmann [*Z. Naturforsch. 34b* (1979) 451] have recently summarized complexes with different polysulfido ligands.

Novel Clusters of Cobalt and Nickel with Organophosphorus Ligands**

By *Dieter Fenske**, *Ramazan Basoglu*, *Johannes Hachgenei*, and *Friedhelm Rogel*

Reactions of transition metal halides with silylated phosphanes have already been reported on by several authors[1]. In some of these reactions the formation of binuclear metal complexes was also observed[2]. We have now even found a simple entry to polynuclear clusters in this way. When $CoCl_2 \cdot 2PPh_3$ is allowed to react with $(Me_3Si)_2PPh$ in tetrahydrofuran (THF), the tetranuclear cluster **1** can be isolated from the products (yield *ca.* 70%)[3a].

$$CoCl_2 \cdot 2PPh_3 + (Me_3Si)_2PPh \xrightarrow[THF]{293\ K} [Co_4(\mu_3\text{-}PPh)_4(PPh_3)_4]$$
1

The dark green compound **1** is diamagnetic. In THF solution it can be reversibly oxidized to $\mathbf{1}^{\oplus}$ and $\mathbf{1}^{2\oplus}$[4]. **1** reacts with Br_2 or I_2 to give $CoX_2 \cdot 2PPh_3$ (X = Br, I). $CHCl_3$, CCl_4 and $C_2H_4Cl_2$ oxidize **1** with formation of $\mathbf{1}^{\oplus}Cl^{\ominus}$. Reaction of **1** in toluene with CH_3COCl above 330 K affords a green oil, crystallization of which furnishes the salt-like product **2** having the composition $\mathbf{1}^{\oplus}[CoCl_3(PPh_3)]^{\ominus}$[3b]. Reaction of **2** with $[(C_4H_9)_4N][PF_6]$ leads to formation of $\mathbf{1}^{\oplus}[PF_6]^{\ominus}$ **3**. The compounds **2** and **3** are paramagnetic ($\mu_{eff} = 4.55$ and $2.50\,\mu_B$, respectively, at 300 K)[5].

In the ^{1}H-NMR spectrum of **2**, broad signals are observed for the phenyl protons of the $[CoCl_3(PPh_3)]^{\ominus}$ anion at $\delta = 13.60$, -3.10 and -3.70[6]. A strong deshielding is found for the phenyl protons of the μ_3-PPh ligands in the cation $\mathbf{1}^{\oplus}$ ($\delta = 15.06$, 11.06, and 10.52), which is less marked in the case of the PPh_3 ligand ($\delta = 7.53$, 6.09, and 6.02). The corresponding signals in the spectrum of neutral **1** appear at $\delta = 6.7$–7.6.

As shown by the X-ray structure analysis, **1** crystallizes together with PPh_3 in the ratio 1:1. The molecular structure of **1** contains a Co_4-cluster. Each surface of this tetrahedral cluster is coordinated by a μ_3-PPh ligand, and each Co atom is bound to a PPh_3 ligand. In **1**, the cluster has a threefold axis (the Co1, P1, and P41 atoms occupy the 6c positions, the Co2, P2, and P3 atoms the 18f positions; as a result, the phenyl ring is statistically disordered at P41). **2** contains a cluster of the same structure as cation, and $[CoCl_3(PPh_3)]^{\ominus}$ as anion. Their structures are reproduced in Figures 1 and 2.

In **1** and $\mathbf{1}^{\oplus}$, each Co atom is surrounded by a distorted tetrahedral array of three μ_3-P atoms and one monodentate coordinated P-atom ((μ_3-P)–Co–(μ_3-P) 103–105, P–Co–(μ_3-P) 114–117°). In turn, the Co atoms form a tetrahedron with the following Co–Co distances: (**1**: Co1–Co2 3 × 258.6(2), Co2–Co2A 3 × 257.1(3) pm; $\mathbf{1}^{\oplus}$: Co1–Co2 256.6(3), Co1–Co3 261.1(6), Co1–Co4 259.6(5), Co2–Co3 254.1(6), Co2–Co4 252.7(6), Co3–Co4 254.9(4) pm); the bond angles in the Co_4 cluster are 59.6–60.1(1)° for **1** and 58.6–61.3(1)° for $\mathbf{1}^{\oplus}$. Consistent with the noble gas rule (60 valence electrons), the Co_4 cluster in **1** has al-

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[**] This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie. We thank Prof. *H. G. von Schnering* for valuable discussions, and the Institut für Kristallographie der Universität Karlsruhe for measuring the crystallographic data.

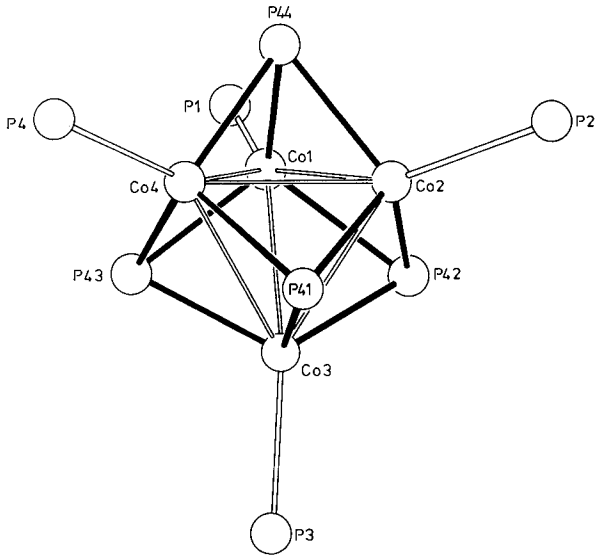

Fig. 1. Molecular structure of **1** and $\mathbf{1}^{\oplus}$ in the crystal (the phenyl groups are not shown for sake of clarity). P1, P2, P3 and P4 signify P-atoms of the $P(C_6H_5)_3$-ligand, P41, P42, P43 and P44 the P-atoms of the μ_3-$P(C_6H_5)$-ligand. **1**: $C_{96}H_{80}Co_4P_8 \cdot P(C_6H_5)_3$, crystals from toluene. Lattice constants (180 K): $a=b=1414.4(3)$, $c=8295.0(30)$ pm, $\alpha=\beta=90$, $\gamma=120°$; space group $R\bar{3}$, $Z=6$. Data collection: Syntex $P2_1$, $Mo_{K\alpha}$ up to $2\theta=45°$; 3098 reflections with $I>1.96\sigma(I)$, empirical absorption correction. Solution of structure: Patterson methods, anisotropic refinement of all atoms (without H) leads with all data to $R_1=0.078$, $R_2=0.066$. **2**: $C_{114}H_{95}Cl_3Co_5P_9$, crystals from ethyl acetate. Lattice constants (293 K): $a=5094.6(31)$, $b=1478.7(4)$, $c=3932.1(11)$ pm, $\beta=132.07(3)°$; space group C2/c, $Z=8$. Data collection: Syntex R3, $Mo_{K\alpha}$, up to $2\theta=45°$; 8703 reflections with $I>1.96\sigma(I)$, empirical absorption correction. Solution of structure: Patterson methods, anisotropic refinement for Co, P, and Cl (rigid phenyl group with C–C 139.5 pm) leads with all data to $R_1=0.084$, $R_2=0.078$ (cf. also Fig. 2) [7].

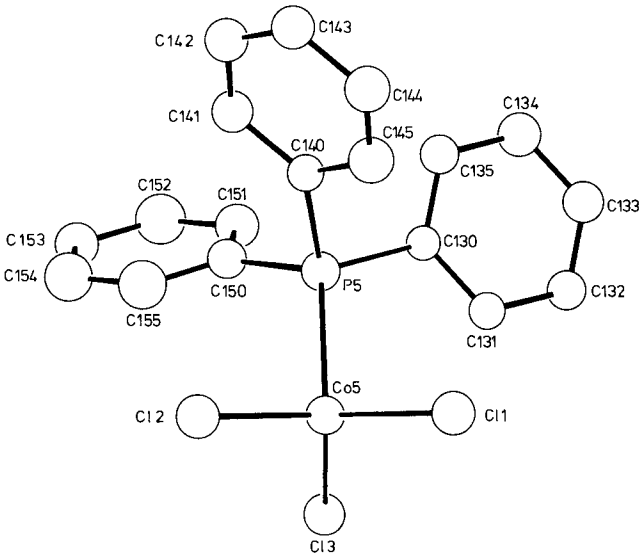

Fig. 2. Molecular structure of the $[CoCl_3(P(C_6H_5)_3)]^{\ominus}$ anion in the crystal of **2**. Bond lengths [pm]: Co5–Cl1 226.9(6), Co5–Cl2 223.8(9), Co5–Cl3 222.2(9), Co5–P5 239.4(8); bond angles [°]: Cl–Co5–Cl 113–116, Cl–Co5–P5 103–105.

most T_d symmetry; in $\mathbf{1}^{\oplus}$ (only 59 valence electrons), on the other hand, the tetrahedron is distorted[8].

In the analogous reaction of $NiCl_2$ with PPh_3 and $(Me_3Si)_2PPh$[3c] the silylphosphane is not completely consumed. Addition of acetyl chloride leads to a change in color from brown to green and formation of a crystalline precipitate. The clusters **4** and **5** can be isolated by fractional crystallization from ethyl acetate.

$[Ni_8Cl_4(PPh)_6(PPh_3)_4]$ **4** $\quad$ $[Ni_8(CO)_4(PPh)_6(PPh_3)_4]$ **5**

The course of the reaction is not known in detail; but the ratio of the products **4** and **5** depends on the reaction time. Apparently **5** predominates in the initial stages of the reaction, and this then reacts with CH_3COCl to give **4**[9]. Conversely, **5** can be prepared by reaction of **4** with sodium amalgam under CO[3c]. Attempts to replace the Cl ligands in **4** by $Br^{\ominus}$ or $I^{\ominus}$ met without success. However, a cluster of the composition $[Ni_8Br_4(PPh)_6(PPh_3)_4]$ can be prepared by reaction of **5** with Br_2[10].

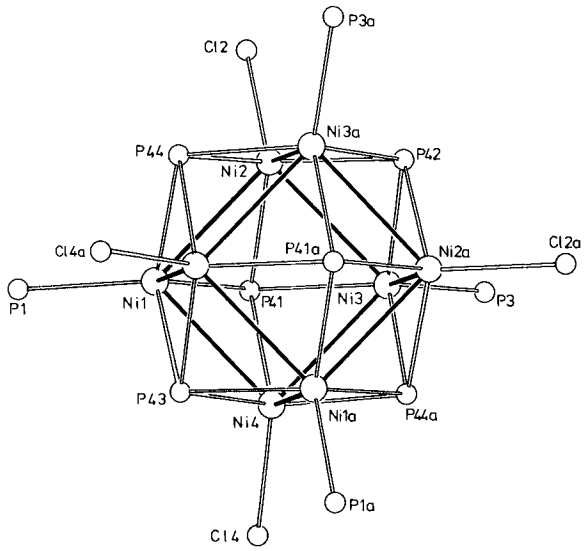

Fig. 3. Molecular structure of the cluster 4 (without phenyl groups). P1 and P3, and P41–P44, respectively, signify the P atoms of the $P(C_6H_5)_3$- and PC_6H_5-ligands. **4**: $C_{108}H_{90}Cl_4Ni_8P_{10}$, crystals from toluene, 4 crystallizes with toluene in the ratio 1:1, space group C2/c. Lattice constants (293 K): $a=1943.7(8)$, $b=2678.4(11)$, $c=2228.8(9)$ pm, $\beta=90.22(3)°$, $Z=4$, $\mu(Mo_{K\alpha})=15.4\ cm^{-1}$. Data collection: Syntex R3, up to $2\theta=45°$; 7695 reflections, 6178 with $I>2\sigma(I)$, empirical absorption correction. Structure solution: Patterson methods, anisotropic refinement of all atoms (without H) lead to $R_1=0.067$, $R_2=0.067$ [7]. Most important bond lengths [pm]: Ni–Ni 259..2–262.1(10), Ni-(μ_4-P) 220.4–222.4(9), Ni1–P1 224.5(9), Ni3–P3 224.7(9), Ni2–Cl2 223.7(9), Ni4–Cl4 225.1(9). Most important angles (±0.2°): Ni–Ni–Ni 89.6–90.3, P1–Ni1–(μ_4-P) 109.5–111.6, (μ_4-P)–Ni–(μ_4-P) 107.5–108.7, Cl2–Ni2–(μ_4-P) 110.3–111.9, Ni–(μ_4-P)–Ni 71.6–72.5.

As can be seen in Figures 3 and 4 the two compounds **4** and **5** each contain a cubic array of eight Ni atoms, each face of which is coordinated by a μ_4-PPh ligand. Ni is surrounded almost tetrahedrally by the ligands bound to it. In **5**, Ni is bound alternately to CO ($\tilde{\nu}CO=1948\ cm^{-1}$) and PPh_3. If the PPh bridge ligand is considered as a 4e-donor, then **5** contains 120 valence electrons and is thus isoelectronic with a cluster of formula $Ni_8(CO)_8(PPh)_6$ already described by *Dahl* et al.[12]. The structure of **4** can be derived from that of **5** by replacing CO by $Cl^{\ominus}$. However, the cluster **4** contains only 116 valence electrons and does not conform to the nobel gas rule. That is, in **4** and **5** there are respectively 20 and 24 electrons available for formation of Ni–Ni bonds. This manifests itself in the Ni–Ni bond lengths, which are markedly shorter in **4** (259.2–262.1 pm) than in **5** (265.3–268.8 pm).

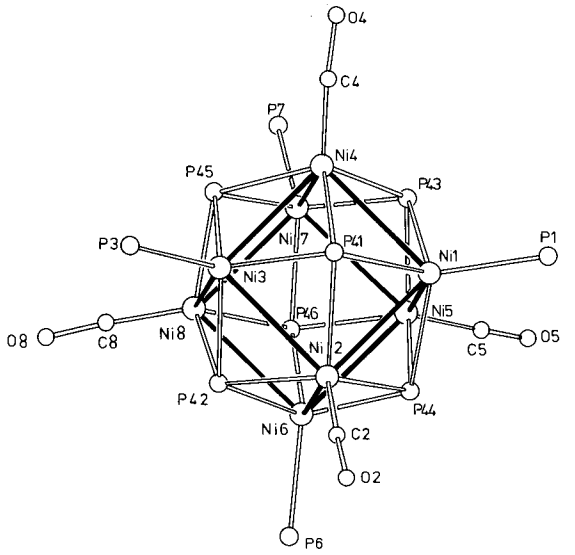

Fig. 4. Molecular structure of the cluster **5** (without phenyl groups). P1, P3, P6, P7, and P41—P46 respectively signify the P-atoms of the $P(C_6H_5)_3$- and PC_6H_5-ligands. **5**: $C_{112}H_{90}O_4Ni_8P_{10}$, crystals from ethyl acetate [11], **5** crystallizes with ethyl acetate in the ratio 1:2, space group $P2_1/c$. Lattice constants (293 K): $a=2471.5(10)$, $b=1561.8(7)$, $c=2893.0(9)$ pm, $\beta=90.45(3)°$, $Z=4$, $\mu(Mo_{K\alpha})=15.2$ cm^{-1}. Data collection: Syntex R3, up to $2\theta=40°$; 11830 reflections, 9350 with $I>2\sigma(I)$, empirical absorption correction. Solution of structure: Patterson methods, anisotropic refinement of all atoms (without H) lead to $R_1=0.088$, $R_2=0.090$ [7]. Most important bond lengths [pm]: Ni—Ni 265.3—268.8(2), Ni—(μ_4-P) 218.0—221.0(3), Ni—P 225.9—228.8(4), Ni—CO 176.2—184.5(15), C—O 109.5—114.2(29). Most important bond angles [°]: Ni—Ni—Ni 88.3—91.5(1), P—Ni—(μ_4-P) 110.7—116.3(1), (μ_4-P)—Ni—C 113.1—116.4(6), Ni—(μ_4-P)—Ni 74.2—76.0(1), Ni—C—O 176.7—179.1(12).

As expected, **5** is diamagnetic; **4**, on the other hand, exhibits paramagnetic behavior and has a temperature-dependent magnetic moment[5] ($\mu_{eff}=2.37$ (300 K), 2.48 (200 K), 2.54 (100 K), 2.44 (25 K), 1.86 (10 K), 1.34 (5 K), $0.94\mu_B$ (4 K)). Formally, the Ni_8 cluster in **4** can be considered to have two different oxidation states: On the one hand, the cluster with the $PPh^{2\ominus}$ and $Cl^{\ominus}$ ligands has the charge $[Ni_8]^{16\oplus}$ and consists of $8\times Ni^{2\oplus}$; on the other, $[Ni_8]^{4\oplus}$ is present if the ligands are regarded as $Cl^{\ominus}$ and PPh^0. In the second case, **4** is a compound which contains nickel in two different oxidation states ($4\times Ni^0$, $4\times Ni^{1\oplus}$), and the magnetic behavior can be explained in terms of an antiferromagnetic coupling of $Ni^{1\oplus}$.

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1·$P(C_6H_5)_3$, 88610-43-9; $\mathbf{1}^{\oplus}$ $Cl^{\ominus}$, 88635-11-4; **2**, 88610-45-1; **3**, 88610-46-2; **4**, 88635-12-5; **4** (bromo derivative), 88635-13-6; **5**, 88610-47-3; $CoCl_2$·2 PPh_3, 14126-40-0; $CoBr_2$·2 PPh_3, 14126-32-0; CoI_2·2 PPh_3, 14056-93-0

[1] E. Abel, J. Sabherwal, *J. Organomet. Chem. 10* (1967) 491.
[2] H. Schäfer, *Z. Anorg. Allg. Chem. 467* (1980) 105.
[3] Procedure: a) $[(CH_3)_3Si]_2PC_6H_5$ (10 mL, 0.037 mol) is added dropwise to a solution of $CoCl_2$·2 $P(C_6H_5)_3$ (23.5 g, 0.036 mol) in anhydrous THF (250 mL) (change in color from blue to green). After 24 h the solvent is removed in a vacuum and the residue recrystallized from toluene. The resulting **1**·$P(C_6H_5)_3$ is isolated in 70% yield.—b) 10 mL acetyl chloride is added to a solution of **1** (3.96 g, 0.002 mol) in toluene (100 mL) and the mixture heated for 3 h at 350 K. The color of the solution changes from green to blue, and a green oil separates out. Crystallization of the oil from ethyl acetate affords **2** in *ca.* 50% yield.—c) A suspension of anhydrous $NiCl_2$ (9.72 g, 0.075 mol) and $P(C_6H_5)_3$ (20 g, 0.076 mol) in THF (250 mL) is treated with 20 mL (0.075 mol) $[(CH_3)_3Si]_2PC_6H_5$. After 4 d the solution is filtered and the solvent removed. To a solution of the residue in toluene (100 mL) is added 20 mL CH_3COCl. After 12 h the crystalline precipitate is washed with CH_3OH and dried in a vacuum. The mixture of **4** and **5** can be separated by fractional crystallization (from ethyl acetate): yield of **4** 60—70%. For conversion into **5**, **4** (4.2 g) is allowed to react with sodium amalgam (0.2 g Na in 40 g Hg) in 100 mL THF under CO atmosphere (color change green→brown). Recrystallization of the precipitate from ethyl acetate furnishes **5** in a yield of 50—60%.
[4] 10^{-3} M solution in tetrahydrofuran (10^{-1} mol $[(C_4H_9)_4N][PF_6]$ as supporting electrolyte): $\mathbf{1} \xrightarrow{0.42\ V} \mathbf{1}^{\oplus} \xrightarrow{1.09\ V} \mathbf{1}^{2\oplus}$.
[5] We thank Prof. *A. Simon* and *Dr. W. Urland*, Stuttgart, for valuable help with the measurement and interpretation of the magnetic properties.
[6] Lim You Yan, *J. Chem. Soc. Faraday Trans. 73* (1977) 446.
[7] Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen, on quoting the depository number CSD 50657, the names of the authors, and full citation of the journal.
[8] Trinh-Toan, W. P. Fehlhammer, L. F. Dahl, *J. Am. Chem. Soc. 94* (1972) 3389; W. A. Neumann, Trinh-Toan, L. F. Dahl, *ibid. 94* (1972) 3383.
[9] Cf. H. Klein, H. Karsch, *Chem. Ber. 109* (1976) 2525.
[10] The bromo derivative crystallizes in the space group C2/c. Lattice constants at 170 K: $a=1934.0(15)$, $b=2573.5(20)$, $c=2256.1(16)$ pm, $\beta=92.12(3)°$, $Z=4$; $2\theta_{max}=40°$, 2735 reflections with $I>2\sigma(I)$, isotropic refinement, $R_1=0.088$, $R_2=0.087$. Ni—Ni 259.2—262.3(5), Ni—(μ_4-P) 220.8—222.9(6), Ni—P 224.6—227.2(6), Ni—Br 237.2—239.0(5) pm.
[11] **5** crystallizes in yet another modification, space group $P\bar{3}$. Lattice constants at 170 K: $a=b=2909.1(10)$, $c=3450.7(25)$ pm, $\alpha=\beta=90$, $\gamma=120°$, $Z=8$, $2\theta_{max}=40°$, 7500 reflections with $I>2\sigma(I)$, $R_1=0.098$, $R_2=0.092$.
[12] L. D. Lower, L. F. Dahl, *J. Am. Chem. Soc. 98* (1976) 5046.

Optically Active α-Arylcarboxylic Acids by Kinetic Resolution: Pyrethroid Acids**

By *Christoph Rüchardt**, *Holger Gärtner*, and *Ulrich Salz*

A recently described method for the preparation of optically active α-arylcarboxylic acids by base-catalyzed reaction of alkyl(aryl)ketenes with optically active alcohols affords good optical yields of the ester that is isolated; however, because of the high reactivity of the ketenes—even when their isolation is circumventable—interfering reactions occur[1,2]. We have now found that optically active α-arylcarboxylic acids **4** and their esters **3** can be obtained in excellent chemical and optical yields if the diastereomeric mixtures of the α-arylcarboxylic acid anhydrides **1** are allowed to react with stoichiometric amounts of the optically active 1-(3-pyridyl)ethanol **2a** or 1-(4-pyridyl)ethanol **2b** in toluene at room temperature.

The results in Table 1 show that the enrichment of an enantiomer of the carboxylic acids can be up to 100% in the esters **3**; in the carboxylic acids **4** formed at the same time, the antipode is enriched. Since the carboxylic acid **4** racemizes again on reconversion into the anhydride **1** with boiling acetic anhydride and pyridine[3], this method is suitable for the complete conversion of a racemic α-arylcarboxylic acid into its optically active ester **3**. A further advantage of the 1-pyridylethanols **2** is that their esters **3** undergo smooth acid-catalyzed hydrolysis without racemization of the alcohol (S_N1) or elimination (E_1); optically pure **2** is recovered[4]. On the one hand, the protonation at nitrogen hinders S_N1 or E_1 reactions in the alcohol moiety,

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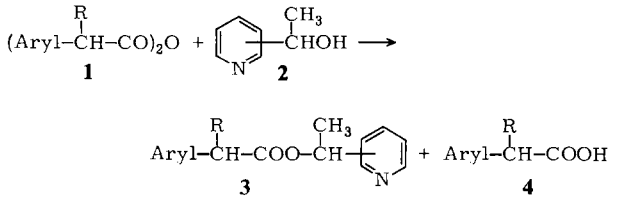


a: 3-Pyridyl; **b**: 4-Pyridyl

Table 1. Reaction of the α-arylcarboxylic acid anhydrides **1** ($c = 0.1$ mol/L) with 1-pyridylethanols **2** in toluene (molar ratio **1** : **2** = 1 : 1) to give esters of type **3** and acids of type **4**.

1	**2**		**3**			**4**	
Aryl	R		T [°C]	Yield [%]	*de* [a] [%]	Yield [%]	*ee* [b] [%]
C_6H_5	CH_3	(*S*)-(−)-**2b**	25	77	74	70	62
C_6H_5	C_2H_5	(*S*)-(−)-**2b**	22	93	82	90	54
C_6H_5	C_2H_5	*rac*-**2b**	22	96	92	—	—
C_6H_5	2-C_3H_7	(*S*)-(−)-**2b**	23	99	76	99	50
C_6H_5	*t*-C_4H_9	(*R*)-(+)-**2b**	23	95	100	89	64
4-$CH_3OC_6H_4$	2-C_3H_7	(*S*)-(−)-**2b**	23	94	82	88	49
4-$CH_3OC_6H_4$	2-C_3H_7	*rac*-**2b**	23	96	94	—	—
4-ClC_6H_4	2-C_3H_7	(*R*)-(+)-**2b**	25	96	74	82	38
4-ClC_6H_4	2-C_3H_7	(*S*)-(−)-**2a**	23	94	70	78	46
4-ClC_6H_4	2-C_3H_7	*rac*-**2b**	24	92	82	—	—

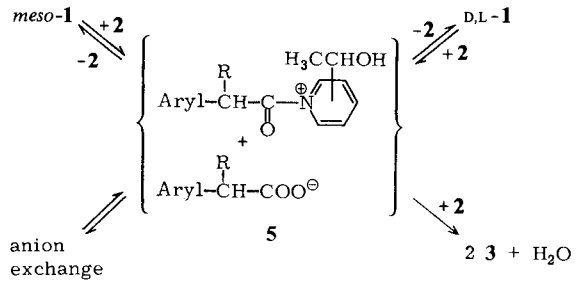
[a] *de* = diastereomeric excess of (*S*,*S*)-**3** (with (*S*)-(−)-**2**) or (*R*,*R*)-**3** (with (*R*)-(+)-**2**) determined by GC; error ±2%. [b] *ee* = enantiomeric excess; with (*S*)-(−)-**2** the (*R*)-carboxylic acid **4** is formed preferentially; determined from $[\alpha]_D$; error ±5%.

and, on the other, increases the quality of the alcohol as leaving group in the ester hydrolysis according to the addition-elimination mechanism ($A_{AC}2$)[5]. Moreover, both enantiomers of the alcohols **2** can easily be obtained by resolution with tartaric acid or dibenzoyltartaric acid[6].

The method is ideally suitable for the production of optically active 2-aryl-3-methylbutyric acids of type **4** (R = 2-C_3H_7, aryl = C_6H_5, 4-Cl-C_6H_4 or 4-CH_3O-C_6H_4), which find use as pyrethroid acids[7] in synthetic insecticides such as the highly effective Fenvalerate[7,8]. The finding that racemic **2** leads to an equal or even somewhat higher diastereomeric excess in **3** than (*S*)- or (*R*)-**2** is indicative of kinetic resolution[3,9]. Kinetic resolution in the reaction of chiral secondary alcohols with an *excess* of α-phenylbutyric acid anhydride in pyridine is already known as the Horeau method for the analytical determination of the absolute configuration of secondary alcohols[3,10]. Conversely it has occasionally also been used for the determination of the configuration of carboxylic acids using optically active menthol as alcohol component[3,10]. The advantage of the 1-pyridylethanols **2** is that, even if only stoichiometric amounts are used, higher optical yields are obtained in the ester **3**, thus making the reaction a preparatively useful one.

To interpret these findings one must assume that the diastereomeric anhydrides **1** equilibrate under the reaction conditions. The essential intermediate for the equilibration and, likewise, for the kinetically decisive acylation step could be **5**. It is even possible that two molecules of **5** participate in the selectivity-determining acylation step. It has not been tested whether base-catalyzed racemization of the anhydride also takes place besides the *meso*-D,L equilibration under the reaction conditions.

Addition of *tert*-amines lowers the optical yields[11]. Lower optical yields are achieved also with amino alcohols such as *N*-methylephedrine or *N*-methylpseudoephedrine[11].



Procedure

2-(4-Chlorophenyl)-3-methylbutyric acid anhydride (4.1 g, 10.0 mmol) is allowed to react with *R*-(+)-**2b** (1.2 g, 10.0 mmol) ($[\alpha]_D^{20} = 46.0$, $c = 0.50$, ethanol, i.e. 92.4 ± 2% *ee*[6b]) in 100 mL toluene for 16 h at 25 °C. Extraction with 2 × 50 mL dil. NaOH, precipitation with conc. HCl, dissolution in ether, washing, drying and removal of the solvent furnishes 1.9 g (82%) (*S*)-(+)-2-(4-chlorophenyl)-3-methylbutyric acid of type **4**, $[\alpha]_D^{20} = 16.5$ ($c = 0.96$, $CHCl_3$), corresponding to an optical yield (*ee*) of 38 ± 5%[7c]. Neutral washing of the toluene solution followed by drying with $MgSO_4$ and removal of the solvent in vacuo affords 2.9 g (96%) 1-(4-pyridyl)ethyl 2-(4-chlorophenyl)-3-methylbutyrate of type **3**, whose diastereomeric ratio was determined by GC (25 m glass capillary SE 20, 200 °C) to be 87 : 13 (*de* = 74%). The product was characterized by elemental analysis, ^{1}H-NMR spectroscopy, and GC.

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CAS Registry numbers:
meso-**1** (Ar = C_6H_5, R = CH_3), 34311-11-0; *dl*-**1** (Ar = C_6H_5, R = CH_3), 88588-25-4; *meso*-**1** (Ar = C_6H_5, R = C_2H_5), 88588-26-5; *dl*-**1** (Ar = C_6H_5, R = C_2H_5), 40348-94-5; *meso*-**1** (Ar = C_6H_5, R = 2-C_3H_7), 88549-54-6; *dl*-**1** (Ar = C_6H_5, R = 2-C_3H_7), 88549-55-7; *meso*-**1** (Ar = C_6H_5, R = *t*-C_4H_9), 88549-56-8; *dl*-**1** (Ar = C_6H_5, R = *t*-C_4H_9), 88549-57-9; *meso*-**1** (Ar = 4-$CH_3OC_6H_4$, R = 2-C_3H_7), 88549-58-0; *dl*-**1** (Ar = 4-$CH_3OC_6H_4$, R = 2-C_3H_7), 88549-59-1; *meso*-**1** (Ar = 4-ClC_6H_4, R = 2-C_3H_7), 88549-60-4; *dl*-**1** (Ar = 4-ClC_6H_4, R = 2-C_3H_7), 88549-61-5; (*S*)-(−)-**2a**, 5096-11-7; *rac*-**2b**, 42732-22-9; (*R*)-(+)-**2b**, 21854-88-2; (*S*)-(−)-**2b**, 54656-96-1; (*S*,*S*)-**3a** (Ar = 4-ClC_6H_4, R = 2-C_3H_7), 88549-73-9; (*R*,*S*)-**3a** (Ar = 4-ClC_6H_4, R = 2-C_3H_7), 88549-74-0; (*S*,*S*)-**3b** (Ar = C_6H_5, R = CH_3), 88549-62-6; (*R*,*S*)-**3b** (Ar = C_6H_5, R = CH_3), 88549-63-7; (*S*,*S*)-**3b** (Ar = C_6H_5, R = C_2H_5), 88549-64-8; (*R*,*S*)-**3b** (Ar = C_6H_5, R = C_2H_5), 88549-65-9; (*R**,*R**)-(±)-**3b** (Ar = C_6H_5, R = C_2H_5), 88588-27-6; (*R**,*R**)-(±)-**3b** (Ar = C_6H_5, R = C_2H_5), 88588-31-2; (*S*,*S*)-**3b** (Ar = C_6H_5, R = 2-C_3H_7), 88549-66-0; (*R*,*S*)-**3b** (Ar = C_6H_5, R = 2-C_3H_7), 88549-67-1; (*R*,*R*)-**3b** (Ar = C_6H_5, R = *t*-C_4H_9), 88549-68-2; (*S*,*S*)-**3b** (Ar = 4-$CH_3OC_6H_4$, R = 2-C_3H_7), 88549-69-3; (*R*,*S*)-**3b** (Ar = 4-$CH_3OC_6H_4$, R = 2-C_3H_7), 88549-70-6; (*R**,*S**)-(±)-**3b** (Ar = 4-$CH_3OC_6H_4$, R = 2-C_3H_7), 88588-28-7; (*R**,*S**)-(±)-**3b** (Ar = 4-$CH_3OC_6H_4$, R = 2-C_3H_7), 88588-32-3; (*R*,*R*)-**3b** (Ar = 4-ClC_6H_4, R = 2-C_3H_7), 88549-71-7; (*S*,*R*)-**3b** (Ar = 4-ClC_6H_4, R = 2-C_3H_7), 88549-72-8; (*R**,*R**)-(±)-**3b** (Ar = 4-ClC_6H_4, R = 2-C_3H_7), 88588-29-8; (*R**,*S**)-(±)-**3b** (Ar = 4-ClC_6H_4, R = 2-C_3H_7), 88588-33-4; (*R*)-**4** (Ar = C_6H_5, R = CH_3, 7782-26-5; (*S*)-**4** (Ar = C_6H_5, R = CH_3, 7782-24-3; (*R*)-**4** (Ar = C_6H_5, R = C_2H_5, 938-79-4; (*S*)-**4** (Ar = C_6H_5, R = C_2H_5, 4286-15-1; (*R*)-**4** (Ar = C_6H_5, R = 2-C_3H_7, 13491-13-9; (*S*)-**4** (Ar = C_6H_5, R = 2-C_3H_7, 13490-69-2; (*R*)-**4** (Ar = C_6H_5, R = *t*-C_4H_9, 13491-16-2; (*S*)-**4** (Ar = C_6H_5, R = *t*-C_4H_9, 13490-71-6; (*R*)-**4** (Ar = 4-$CH_3OC_6H_4$, R = 2-C_3H_7), 88588-30-1; (*S*)-**4** (Ar = 4-$CH_3OC_6H_4$, R = 2-C_3H_7), 55332-36-0; (*R*)-**4** (Ar = 4-ClC_6H_4, R = 2-C_3H_7), 63640-09-5; (*S*)-**4** (Ar = 4-ClC_6H_4, R = 2-C_3H_7), 55332-38-2

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[4] **3a** (10.3 mmol; aryl = C_6H_5, R = C_2H_5; *R*,*S* : *S*,*S* = 89 : 11, corresponding to 78% *de*) was completely hydrolyzed (GC control) in 30 mL boiling dioxane/H_2O (2 : 1 v/v) with 3 g acid ion-exchanger I (Merck). 83% (*R*)-(+)-2-phenylbutyric acid (*R* : *S* = 84 : 16, corresponding to 68% *ee*) is isolated from the solution. 78% (*S*)-(−)-**2b** is recovered from the ion-exchanger with HCl, with a maximum loss of optical purity of 4%.

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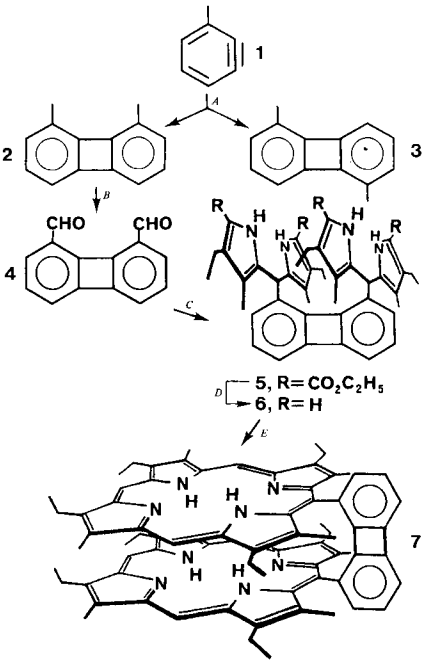
A Biphenylenediporphyrin: Two Cofacially Arranged Porphyrins with a Biphenylene Bridge**

By *Chi K. Chang** and *Ismail Abdalmuhdi*

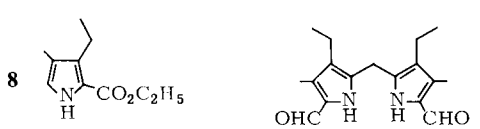
Cofacial diporphyrins and their metal complexes, first synthesized in 1977, have found interesting applications in mediating the 4e path of O_2 reduction on graphite electrodes[1,2] as well as in modeling light-induced charge separation in photosynthetic reaction centers[3]. To date, most cofacial dimers have been prepared by linking two porphyrin rings via an amide (or ester) bond[4]. While this method of covalent linkage is synthetically straightforward, the yields from the lengthy sequence have been low. More serious is the fact that the long-term stability of the amide bond is low in the acid environments present in many potentially useful electrochemical O_2-reduction systems, e.g., fuel cells. It is therefore worthwhile to explore other approaches to synthesize dimeric porphyrins. We report here the synthesis of a novel biphenylene cofacially arranged diporphyrin **7**.

For diporphyrins used in electrocatalytic O_2-reductions, the interporphyrin distance has been shown to be critical. The proven optimum length consists of four C atoms[1,2]. Bearing this in mind, a biphenylene having two porphyrins attached at the 1 and 8 positions should be very attractive. 1,8-Biphenylenedicarboxaldehyde, prepared from the dimethyl precursor, could serve as a convenient starting material. 3-Methylbenzyne **1**[4] was condensed in situ to yield a mixture of 1,8- **2** and 1,5-dimethylbiphenylene **3**. The separation of the two isomers was found to be much simpler if the mixture was converted first to the dialdehydes and then chromatographed. Attempts to condense 1,8-biphenylenedicarboxaldehyde with a mixture of pyrrole and benzaldehyde invariably produced only tetraphenylporphyrin and untractable materials. The 1,8-dialdehyde **4**, however, reacted cleanly with ethyl 3-ethyl-4-methyl-2-pyrrolecarboxylate **8**[6] to give almost quantitatively the bis(dipyrrylmethane) **5**. The tetraester **5** was saponified and the acid **6** decarboxylated. Unlike common α-unsubstituted dipyrrylmethanes, **6** did not yield any porphyrin when allowed to react with dipyrrylmethane-5,5′-dialdehydes such as the (5,5′-diformyl-4,4′-dimethyl-3,3′-diethyl-2,2′-dipyrryl)methane **9** in 0.4% HI/HOAc (MacDonald method). However, if the same reaction was carried out in 0.4% $HClO_4$/methanol, the desired diporphyrin **7** was obtained, surprisingly in nearly 20% yield.



Scheme 1. *A*) See [4b]. *B*) See [5]. *C*) **4** + **8** (molar ratio 1:4), HCl, in EtOH, 1 h reflux. *D*) **5** + NaOH; $H^{\oplus}$; 2-amino ethanol, 180°C. *E*) **6** + **9** in 0.4% $HClO_4$/MeOH, 5 h, RT; *o*-chloranil.

The ^{1}H-NMR spectrum of **7** shows two sharp singlets for the ring methyl groups since the four methyl groups flanking the biphenylene are shielded by the six-membered rings and shifted ca. 0.3 ppm upfield[7]. The magnitude of this shift is notably smaller compared to other *meso*-phenyletioporphyrins (> 1 ppm)[8]. We consider this as unequivocal proof of the theoretical prediction that the six-membered rings in biphenylene should have a comparatively small diamagnetic ring current[9]. The NH protons appear at a position which agrees well with previously studied, closely-spaced cofacial diporphyrins ($\delta \approx -7.6$)[3]. The cofacial configuration of **7** is also indicated by its UV/VIS spectrum which shows a Soret peak at 378 nm (cf. 402 nm for a *meso*-phenyletioporphyrin). Such blue shifts can be understood in terms of exciton interactions in the diporphyrins[3].



The interplanar distance of the diporphyrins may be estimated by studying the dipolar interaction of two Cu^{2+} centers[10]. As shown in Figure 1, the EPR spectrum displays a seven-line parallel hyperfine pattern with a zero-field splitting of 0.043 cm^{-1}, corresponding to a Cu···Cu distance of ca. 4.1 Å. The most unusual feature of the EPR

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spectrum, however, is the unexpectedly intense signals associated with the half-field transition ($\Delta M_s = \pm 2$). According to theory, the intensity of the half-field transition is determined by the strength of the dipolar interaction. Recently *Eaton* and *Eaton*[11] calculated that the relative intensity defined by the ratio (intensity of $\Delta M_s = \pm 2$)/(total intensity of $\Delta M_s = \pm 1$) should be approximately $20/r^6$, where r is the interspin distance in Å. Assuming there is no gross distortion of the porphyrin rings, their equation estimates the Cu···Cu distance in the dicopper complex of **7** to be <2 Å, a highly unlikely situation. This issue will have to be resolved by an X-ray structure determination.

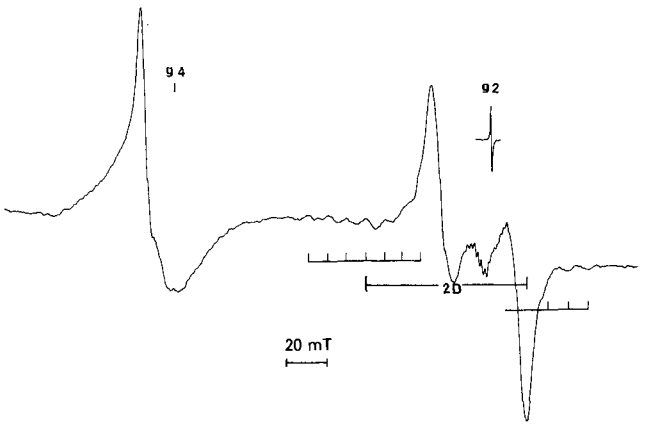

Fig. 1. X-band EPR spectrum of Cu(II)-Cu(II) complex of diporphyrin **7** in toluene at -150°C, $c \approx 1$ mmol/L. Modulation amplitude = 1 mT; $\nu = 9.2$ GHz. D is half the distance between the centers of the parallel absorptions. $g_{\parallel} = 2.18$, $g_{\perp} = 2.05$.

The dicobalt complex of **7** has been synthesized, and preliminary study indicates that a pyrolytic graphite- surface coated by this cobalt diporphyrin is indeed able to reduce O_2 almost exclusively via the 4e path in 0.5 M aqueous trifluoroacetic acid[12].

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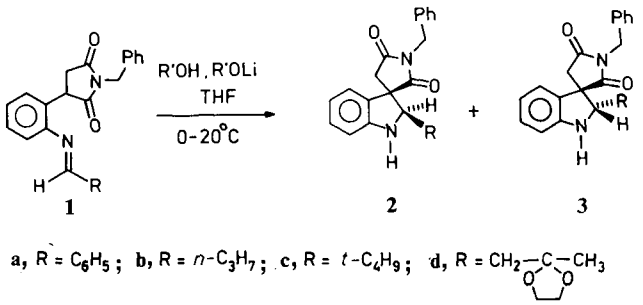
Highly Enantioselective Synthesis of a 2,3-Dihydroindole Mediated by *N*-Methylephedrine

By *Robert Jan Vijn, W. Nico Speckamp*, Bart S. de Jong,* and *Henk Hiemstra*

The single-step synthesis of enantiomerically pure compounds from prochiral educts via the intermediary of a chiral catalyst is the pinnacle of asymmetric synthesis[1]. Reactions that approach such enzymatic processes are still scarce[2]. Here, we wish to communicate the discovery of such a reaction in the course of our investigations of the synthesis of dihydroindoles[3], valuable intermediates in the total synthesis of mitomycins and indole alkaloids[4,8].

Cyclization of azomethines **1** to afford the 2,3-dihydroindoles **2** and **3** proceeds with lithium alkoxide or sodium alkoxide in the presence of the corresponding alcohol in tetrahydrofuran (THF) at 0—20°C. If a bulky secondary or tertiary alcohol is used, the predominant product is the *cis*-2,3-dihydroindole **2**, with less than 10% of the *trans*-isomer **3** being formed[3].

We recently reported[5] that low asymmetric induction (*ee* 17—31%) results if a chiral alcohol, i.e. (−)-menthol or (−)-borneol, is used in this reaction[5]. The degree of enantioselectivity showed little dependence on the structure of chiral alcohol or azomethine, the nature of the cation (Li or Na), or on temperature.



a, R = C_6H_5; **b**, R = n-C_3H_7; **c**, R = t-C_4H_9; **d**, R = CH_2—C(O)(O)—CH_3

We report here the use of chiral β-amino alcohols, which have already been successfully employed as bifunctional catalysts in chiral base catalysis[6]. Although quinine and (*S*)-*N*-methylprolinol gave very low chemical and/or enantiomeric yields, the results with derivatives of ephedrine were good (Table 1). Treatment of the azomethine **1b** with the reagent derived from 1 equiv. of *n*BuLi and 2.5 equiv. of (+)-(1*S*,2*R*)-*N*-methylephedrine **4b** in THF afforded (−)-2,3-dihydroindole **2b** in 50% yield and in more than 95% *ee*[7] (Table 1; entry 4); we were unable to detect the other enantiomer in the ^{1}H-NMR spectrum of the crude product[5,7]. Likewise, (−)-(1*R*,2*S*)-*N*-methylephedrine **5b** yielded the enantiomerically pure (+)-enantiomer of **2b** (entry 5).

An unfortunate feature of this asymmetric synthesis is its extreme sensitivity to small structural variations in substrate and catalyst system. Replacing $Li^{\oplus}$ with $Na^{\oplus}$ leads to a drastic reduction in *ee* (entry 6). Ephedrine **4a** (entries 2, 3) and *N*-benzoylephedrine **4f** (entry 10) are useless as chiral catalysts, whereas substitution of the *N*-methyl group of **4b** with larger groups is also detrimental (entries 7—9). Finally, the nature of R in the azomethine **1** appears to be very important (entries 1, 4, 11, and 12).

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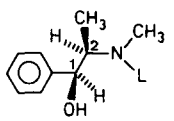
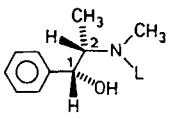
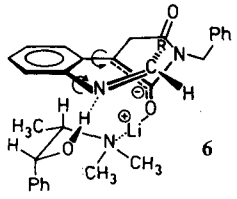


4 a-f



5 a,b



6

Table 1. Enantioselective synthesis of dihydroindoles **2** from azomethines **1** [a]. Cation: $Li^{\oplus}$.

Entry	Azomethine	Catalyst [b]	Prod.	Yield [%] [c]	*ee* [%] [d]	Sign of rotation ($CHCl_3$)
1	**1a**	**4b** L = CH_3	**2a**	53	< 10	
2	**1b**	**4a** L = H	**2b**	51	12	(+)
3 [e]	**1b**	L = H	**2b**	57	< 10	
4	**1b**	**4b** L = CH_3	**2b**	50	> 95	(−)
5	**1b**	**5b** L = CH_3	**2b**	50	> 95	(+)
6 [e]	**1b**	L = CH_3	**2b**	30	20	(+)
7	**1b**	**4c** L = C_2H_5	**2b**	64 [c]	73	(−)
8	**1b**	**4d** L = $CH_2CH_2OCH_3$	**2b**	60	38	(−)
9	**1b**	**4e** L = CH_2Ph	**2b**	48	26	(−)
10	**1b**	**4f** L = COPh	**2b**	44	< 10	
11	**1c**	**4b** L = CH_3	**2c**	70	37	(−)
12	**1d**	**4b** L = CH_3	**2d**	57	50	(−)

[a] Experimental procedure: [7]. [b] **4a** and **5a** are commercially available; **4b–f** and **5b** were synthesized from **4a** and **5a** by either reductive methylation (**4b**, **5b**) [9] or by acylation (**4f**), followed by $LiAlH_4$ reduction (**4c–e**). [c] Isolated yields except for entry 7, for which the ^{1}H-NMR yield is given. [d] Determined by ^{1}H-NMR spectroscopy using Eu(hfc)$_3$ [5, 7]. [e] Cation: $Na^{\oplus}$.

Mechanistically, this ring-closure reaction must be viewed as a disrotatory 1,5-electrocyclization[3, 10]. To account for the formation of the *cis* product we assume that ring closure occurs from the *Z*-azomethine geometry and that the imide enolate has the enolate oxygen directed toward the azomethine, both moieties being arranged in a helix-type conformation. The favorable influence of the hydroxy group is most probably the result of hydrogen bonding with the azomethine nitrogen (O–H···N) in the transition state. Furthermore, in the highly structured transition state the tertiary amine function of the chiral auxiliary is bound via $Li^{\oplus}$ to the enolate oxygen as shown in **6**. This model accounts for the failure of $Na^{\oplus}$ (entry 6) and of the *N*-benzoyl group (entry 10) to induce high *ee* values. Due to the weak Lewis acidity of $Na^{\oplus}$ and the weak Lewis basicity of an amide nitrogen the interaction between enolate and catalyst is loosened in both cases.

Since the conversion of *rac*-**2d** into *rac*-vindorosine has previously been reported[8], the present result can be formally regarded as an enantioselective synthesis of this alkaloid.

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[7] *Procedure:* To a well stirred solution of (1*S*,2*R*)-*N*-methylephedrine **4b** (270 mg, 1.63 mmol) ($[\alpha]_{578}^{RT} = +25$ ($c = 6$, EtOH)) in 5 mL THF under nitrogen at 0°C was added 0.40 mL of a 1.6 N solution of *n*BuLi (0.64 mmol) in hexane. Two minutes later a solution of azomethine **1b** (210 mg, 0.63 mmol) in 1 mL of toluene was added. The resultant blue mixture slowly turned red and was stirred for 45 min at 0°C. 5 mL of 2 N HCl was then added and the mixture extracted with ether (3 × 10 mL). The ether solution thus obtained was dried (Na_2SO_4) and evaporated to leave a light yellow oil (110 mg). Purification via column chromatography [SiO_2 (70–150 mesh), EtOAc, hexane 1:2] afforded 104 mg (0.31 mmol, 50%) of **2b** as light yellow crystals, m.p. 118–119°C (EtOAc/hexane); m.p. (*rac*-**2b**) 125–126°C [3, 8]. $[\alpha]_{578}^{RT} = -71$ ($c = 5.25$, $CHCl_3$); IR (KBr): 3320 (NH), 1760 and 1685 (C=O), 1600, 1385, 1340, 1165, 935, 695 cm^{-1}. ^{1}H-NMR (250 MHz, $CDCl_3$): $\delta = 7.45–6.65$ (m, 9H), 4.70 (d, 1H, $J = 14$ Hz, CH_aH_bPh), 4.61 (d, 1H, $J = 14$ Hz, CH_aH_bPh), 3.85–3.70 (m, 2H, NH and >CH–*n*Pr), 3.17 (d, 1H, $J = 19$ Hz, $-CH_aH_bCON<$), 2.70 (d, 1H, $J = 19$ Hz, $-CH_aH_bCON<$), 1.7–1.1 (m, 4H, CH_2CH_2), 0.79 (t, 3H, CH_3). Addition of Eu(hfc)$_3$ did not change the ^{1}H-NMR spectrum (in the case of the racemic compound the signal originally at $\delta = 3.17$ was split into two doublets of equal intensity).

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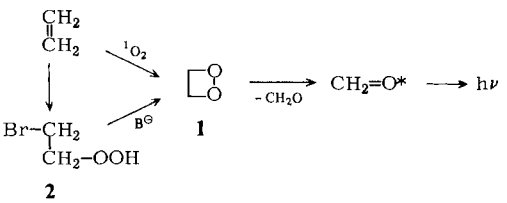
1,2-Dioxetane: Synthesis, Characterization, Stability, and Chemiluminescence**

By *Waldemar Adam** and *Wilhelm J. Baader*

To the best of our knowledge[1], the parent 1,2-dioxetane **1** has been observed only as a transient species in the gas phase via the formaldehyde fluorescence arising from the cycloaddition of singlet oxygen to ethene[2]. The statement ... "isolation and characterization of 1,2-dioxetane still remain a challenge" ...[3] encouraged us to try to prepare the parent 1,2-dioxetane. Here, we report its synthesis, characterization, stability, and chemiluminescence[4].



Synthesis: After photosensitized singlet-oxygenation of ethene in trichlorofluoromethane at −40°C and in the gas phase both failed to produce even traces (monitored by chemiluminescence) of dioxetane **1**, we returned to the now classical Kopecky method[5]. A solution of 2.82 g (20.0 mmol) 1-bromo-2-hydroperoxyethane (**2**)[6] in 20 mL dichloromethane and a solution of 8.00 g (143 mmol) KOH in 20 mL water was vigorously mechanically stirred for ca. 15 min: the mixture was then warmed up from 0°C to 20°C. The organic phase was washed with 10 mL cold water, dried over $MgSO_4$, and the 1,2-dioxetane **1** distilled as a CH_2Cl_2 solution at 0°C/100 torr to 20°C/10 torr. Thin

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layer chromatography (silica gel/CH_2Cl_2) gave a peroxide spot at $R_F = 0.58$ (positive KI/HOAc test). Attempts to remove the CH_2Cl_2 by distillative fractionation failed because of the volatility and thermal lability of **1**. In all subsequent operations the dioxetane was therefore handled in CH_2Cl_2 solution. The yield of the dioxetane was estimated as ca. 0.1% by iodometric titration.

Characterization: Solutions of **1** in CH_2Cl_2 exhibited direct chemiluminescence, which was significantly enhanced by the presence of 9,10-dibromoanthracene (DBA). Control experiments with hydroperoxide **2** confirmed that the latter displayed negligible chemiluminescence under comparable conditions. The 400 MHz ^{1}H-NMR and 100 MHz ^{13}C-NMR spectra of a CD_2Cl_2 solution of **1** at -40 °C exhibited the expected signals at $\delta = 5.38$ and $\delta = 76.14$, respectively, which both disappeared after 1 h at 40 °C. The characteristic singlet of formaldehyde (expected decomposition product) was observed at $\delta = 9.60$ in the ^{1}H-NMR spectrum. These data corroborate the proposed dioxetane structure **1**.

Stability: The activation parameters of dioxetane **1** were determined by DBA-enhanced chemiluminescence[7]. Unfortunately, **1** is very prone to catalytic dark decomposition; hence, for reliable and reproducible kinetic data the activation data had to be assessed from the temperature dependence of the initial chemiluminescence intensities[7] (Table 1). Clearly, the normal chemiluminescence method (values in parentheses) results in considerable catalytic dark decomposition, as witnessed particularly by the very low activation entropy. However, the free energy of activation appears to be a more reliable measure of thermal stability (Table 1). At 343 K a half-life $t_{1/2} = 1.1$ min is extrapolated from these rate data. Compared to tetramethyl-1,2-dioxetane **3**, for which $t_{1/2} = 45$ min at 343 K[7], the parent 1,2-dioxetane **1** is, as predicted[8], considerably less stable.

Table 1. Activation parameters and excitation yields for the thermal decomposition of 1,2-dioxetane **1** in toluene and, for comparison, those for tetramethyl-1,2-dioxetane **3** in benzene. For the values in parenthesis see text.

	ΔH^+ [kcal/mol]	ΔS^+ [cal mol^{-1} K^{-1}]	ΔG^+ (343 K) [kcal/mol]	Φ^S [a] $\times 10^4$	Φ^T [b] $\times 10^2$	Φ^T/Φ^S
1	22.1 ± 0.3 [c]	−3.9	23.3	0.03 ± 0.01	0.2 ± 0.05	700
	(18.9 ± 0.8) [d]	(−12.8 ± 1.6)	(23.4)			
3	26.9 ± 0.1	3.7 ± 0.3	25.8	25 ± 14	35 ± 15	140

[a] Determined from DPA fluorescence via Stern-Volmer kinetics [9]. [b] Determined from DBA fluorescence via Stern-Volmer kinetics [9]. [c] Determined from the temperature dependence of the initial chemiluminescence intensities monitored by DBA-fluorescence [7]. [d] Determined from the time profile of the DBA-fluorescence intensity at various temperatures [7]. [e] Taken from [7] and [9].

Chemiluminescence: Direct chemiluminescence could be observed, but was too weak for quantitative measurements. For this reason energy transfer chemiluminescence with 9,10-diphenylanthracene (DPA) was used to determine singlet excitation yields (Φ^S_{DPA}) and DBA to determine triplet excitation yields (Φ^T_{DBA})[9] (Table 1). Unquestionably, the excitation yields are dramatically lower than those of the tetramethyl-1,2-dioxetane **3**; but, like **3**, the spin state selectivity (Φ^T/Φ^S) for triplet excitation is highly favored. The thermal stability and excitation yields increase with methyl substitution.

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1, 6788-84-7; **2**, 88510-96-7; ethene, 74-85-1; hydrogen peroxide, 7722-84-1

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[6] **2** was prepared in 35% yield by allowing ethene to react with 1,3-dibromo-5,5-dimethylhydantoin and hydrogen peroxide; colorless liquid, b.p. = 30 °C/0.1 torr, 97% peroxide titer by iodometry; IR (CCl_4): $\nu = 3420$ cm^{-1} (s, −OOH); ^{1}H-NMR ($CDCl_3$, 90 MHz): $\delta = 3.62$ (t, $J = 6.0$ Hz, 2H), 4.30 (t, $J = 6.0$ Hz, 2H), 8.90 (br. s, 1H, −OOH); ^{13}C-NMR ($CDCl_3$, 22.6 MHz): $\delta = 28.46$ (t, C−Br), 76.21 (t, C−OOH).
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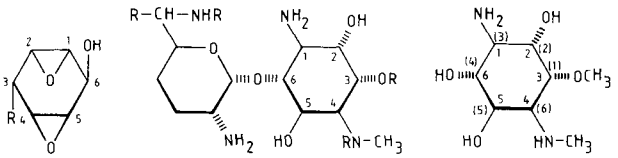
Total Synthesis of a Fortimicin Aglycone**

By *Jürgen Schubert, Reinhard Schwesinger,* and *Horst Prinzbach**

Efficient methods have been developed for the synthesis of a broad spectrum of *cis*-1,3- and *cis*-1,4-(deoxy)inosadiamines using (deoxy)anhydroinositols such as **1** (R = H, OH), which are readily accessible from benzene[1]. Such *cis*-1,4-(deoxy)inosadiamines constitute the aglycone components of several novel, highly effective and structurally simple aminoglycosidic antibiotics (fortimicins **2**[2], istamycins[3], sannamycins[4]).



1 **2** **3**

Herein we report on a convenient entry to enantiomerically pure 3-de-*O*-methylfortamine **11a** starting from 1,2:4,5-dianhydro-*epi*-inositol **1** (R = OH), which is also useful for the total synthesis of chemically modified fortimicins[5]. (In the formula of fortamine **3**, both the "numbering for fortimicin" as well as the "numbering for inositol" is given.) The procedure outlined in Scheme 1 excels in the high selectivity of the epoxide-opening (in **4/5d**) and in the efficient resolution (chromatographic separation of the diastereomeric (*R*)-(+)-1-phenylethylamine adducts **9a/10a**); it makes allowance for the fact that two different *N*-functions could not be selectively introduced via **1** owing to insufficient kinetic differentiation in the separate steps[1,6]. The bisurethane **4** prepared by reaction of **1** with methyl isocyanate (dioxane, 100 °C, 3 h, 95%, m.p. = 203–205 °C[7]), is cyclized regiospecifically by strong, weakly nucleophilic bases, preferably tris(dimethylamino)methyliminophosphorane[8] (acetonitrile, 60 °C, 3 h), with attack at C-1 to give the oxazolidone *rac*-**5a**. The, a priori, possi-

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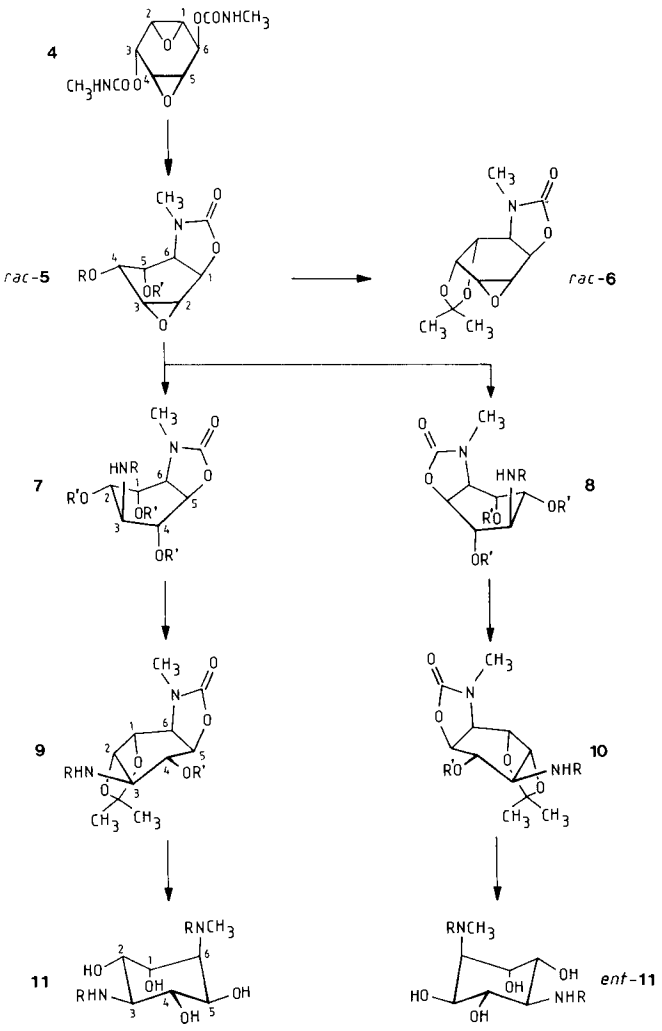
ble competition[9] of attack at C-2 is not at all detectable (<2%). However, transesterification to a mixture of the four components *rac*-**5a**—**d** (together 97%) must be bargained with. Treatment with sodium ethoxide/ethanol (60°C, 1.5 h) furnishes pure *rac*-**5d** (72–75%, m.p. 152–155°C (not optimized), together with up to 5% of the adduct of $C_2H_5O^{\ominus}$ to C-3)[10]. Beyond expectation, is the specificity with which the "half-chair" *rac*-**5d** (D_2O, $J_{3,4}=1.0$, $J_{4,5}=4.0$, $J_{5,6}=3.5$ Hz) is substituted at C-3 by (*R*)-(+)-1-phenylethylamine (and by other nucleophiles such as $C_2H_5O^{\ominus}$, $N_3^{\ominus}$) to give **7a/8a** (boiling 1-propanol, 3 h, almost quantitative). Under the same conditions, the opening of the epoxide ring in the acetal *rac*-**6** is unselective (or more favored at C-2). Separation of the ^{1}H-NMR spectroscopically distinguishable diastereomers **7a/8a** (δ(3-H)=2.80/2.51; $J_{2,3}=4.0/3.0$, $J_{3,4}=9.0/10.0$, $J_{4,5}=8.5/9.5$ Hz), which are also characterized as the triacetates **7b/8b** (δ(3-H)=2.93/2.50; $J_{2,3}=5.0/2.0$, $J_{3,4}=7.5/8.0$, $J_{4,5}=8.5/10.0$ Hz), was accomplished by column chromatography (silica gel, $CHCl_3/CH_3OH$/triethylamine 25:1:1, each isolated in 46% yield); it is, nevertheless, more conveniently carried out via the conventionally prepared (2,2-dimethoxypropane, 1.2 equiv. *p*-toluenesulfonic acid, 2 h, 80°C, 95%) acetals **9a/10a**. After crystallization of ca. 80% **10a** ($CHCl_3$/ether, m.p. = 142°C), pure **9a** (m.p. = 191°C) can be isolated from the mother liquor by "rapid chromatography" (in 10—15 g amounts). According to the ^{1}H-NMR spectra, **9a/10a** and their acetates **9b/10b** preferably exist as the "half-chair" conformers with quasiequatorial substituents on C-3/C-4 ($J_{3,4}=12.0$–12.5 Hz). As in **7a/8a**, the NHR moiety in **9a/10a** also remains unchanged on acetylation.



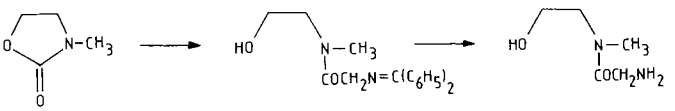
Scheme 1. Substituents of the compounds *rac*-**5**, **7**, **8**, **9**, **10**, **11** and *ent*-**11**.

rac-**5**	**a**	**b**	**c**	**d**	
R	CONHMe	H	CONHMe	H	
R′	H	CONHMe	CONHMe	H	
7, 8	**a**		**b**		
R	(*R*)-CHMePH		(*R*)-CHMePh		
R′	H		Ac		
9, 10	**a**	**b**	**c**	**d**	**e**
R	(*R*)-CHMePh	(*R*)-CHMePh	(*R*)-CHMePh	H	Cbz
R′	H	Ac	$MeO(CH_2)_2OCH_2$	H	H
11, *ent*-**11**		**a**	**b**		
R		H	Cbz		

The primary amines **9d/10d** (=*ent*-**9d**) (as sulfates) are liberated in pure form ($J_{3,4}=12.5$ Hz) in yields of 89–95% from **9a/10a** by hydrogenation with Pd/C (10%) in methanol (0.3 equiv H_2SO_4, 1 bar H_2, 20°C, 24 h). After selective protection of the NH_2 groups with benzyl chloroformate (acetone/water 1:1, sodium carbonate, 20°C, 1 h, 82%), with **9e/10e** (≡*ent*-**9e**) (m.p. = 93–95°C), derivatives of **11a**/*ent*-**11a** are present in which only the 4-OH group is free (e.g. for glycosidation to **2**).

The (tentative) assignment of the diastereomeric pairs **7/8** and **9/10** in the scheme is based on a comparison of the $[\alpha]_D^{25}$ values for natural fortamine **3** (−88, water, $c=1.0$)[11] and the two de-*O*-methyl derivatives **11a**/*ent*-**11a** (−74, +75) obtained by hydrogenation of **7a/8a** and hydrolysis. The latter are liberated from their sulfates (diammonium salts, D_2O, $J_{1,2}=3.0$, $J_{2,3}=J_{3,4}=9.0$, $J_{4,5}=8.5$, $J_{5,6}=5.0$, $J_{6,1}=4.5$ Hz). There is also a correlation between the $[\alpha]_D^{25}$ values of bis-Cbz-fortamine (+47, methanol, $c=1.0$)[12] and the bis-Cbz-derivatives **11b**/*ent*-**11b** (+56, −57).

The 4-*N*-glycyl moiety, essential for the therapeutic activity of fortimicin A, can be incorporated by specific 4-*N*-acylation[13]. As alternative, reaction of the model compound **12** with lithiated *N*-benzhydrylidenemethylamine[14] has been investigated. In preliminary experiments (3 equiv. reagent, ether, −20°C, 10 min) the protected, oily *N*-glycyl derivative **13** was isolated in 50–60% yield and hydrolyzed to **14** (aq. methanol/HCl). The analogously protected glycyl derivative was obtained (50–60%) from **9c**.



12 **13** **14**

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1, 50473-98-9; **4**, 88563-84-2; (*rac*)-**5a**, 88563-85-3; (*rac*)-**5b**, 88563-86-4; (*rac*)-**5c**, 88563-87-5; (*rac*)-**5d**, 88563-88-6; (*rac*)-**6**, 88563-89-7; **7a**, 88563-90-0; **7b**, 88563-91-1; **8a**, 88642-98-2; **8b**, 88642-99-3; **9a**, 88563-92-2; **9b**, 88563-93-3; **9d**, 88563-94-4; **9e**, 88563-95-5; **10a**, 88643-00-9; **10b**, 88643-01-0; **10c**, 88643-59-8; **10e**, 88643-02-1; **11a**, 88563-96-6; (*ent*)-**11a**, 88643-03-2; **11b**, 88563-97-7; (*ent*)-**11b**, 88643-04-3; **12**, 19836-78-3; **13**, 88563-98-8; **14**, 86150-30-3; (*R*)-(+)-1-phenylethylamine, 3886-69-9; *N*-benzyhydrylidenemethylamine, 13280-16-5.

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Synthesis of New Amorphous Metallic Spin Glasses M_2SnTe_4 (M = Cr, Mn, Fe, Co): Solvent Induced Metal-Insulator Transformations**

By *Robert C. Haushalter*, Charles M. O'Connor, Jeanne P. Haushalter, Arun M. Umarji,* and *Gopal K. Shenoy*

The physical properties of amorphous materials are often vastly different from those of their crystalline counterparts. Although most amorphous solids are prepared by rapid thermal quenching, or by pyrolytic or sputtering techniques, chemical methods involving rapid precipitation also produce non-crystalline materials[1]. We report a new, potentially general method for the preparation of novel amorphous materials based on the oxidation of main-group metal polyanions[2] by transition-metal cations in solution.

$$n(M_A^{x+}) + m(M_B^{y-}) \longrightarrow (M_A)_n(M_B)_m$$

By adjusting the ratio n : m such that $x + y = 0$, the neutral product precipitates. With this method, the compounds M_2SnTe_4 (M = Cr, Mn, Fe, Co) have been prepared from M^{2+} and $SnTe_4^{4-}$; however, we focus here on the iron system Fe_2SnTe_4.

When solutions of anhydrous $FeBr_2$ and orange K_4SnTe_4 in methanol are mixed at $-20\,^\circ C$, a black precipitate of composition Fe_2SnTe_4 (elemental analysis) immediately forms. X-ray powder diffraction (XRD) studies indicate that the compound is amorphous (Fig. 1a; A). Pressed powder samples of Fe_2SnTe_4 and Co_2SnTe_4 appear metallic and have low resistivities (Fe_2SnTe_4; $\rho \approx 5 \times 10^{-2}\ \Omega \cdot cm$; Co_2SnTe_4: $\rho \approx 6 \times 10^{-4}\ \Omega \cdot cm$ at 300 K). The practically identical ^{57}Fe Mössbauer spectra of Fe_2SnTe_4 and $FeTe_2$ at 77 K (Table 1) are consistent with the formation of Fe–Te bonds. Samples of Fe_2SnTe_4 yield only barely detectable Mössbauer effects (^{57}Fe, ^{119}Sn) at 300 K, presumably due to very large thermal motion in the highly disordered solid. Below 12 K Fe_2SnTe_4 orders magnetically to form a "spin glass"[3] state, characterized by direct current magnetization (Fig. 1b) and alternating current susceptibility behavior and by the dependence of the thermoremanent magnetization on magnetic field, time, and temperature[4]. Mössbauer measurements at 4.2 K indicate magnetic ordering at both the ^{57}Fe and ^{119}Sn sites, showing that both belong to the same phase and not to the respective binary tellurides[4]. Heating to 600 °C for 24 h leads to decomposition

$$Fe_2SnTe_4 \longrightarrow FeTe_2 + FeTe + SnTe$$

to the thermodynamically more stable crystalline tellurides (Fig. 1a: B). Susceptibility measurements on the thermolysis products FeTe and $FeTe_2$ show the expected antiferromagnetic transitions (Fig. 1c).

Strong donor ligands selectively cleave the Fe–Te bonds in Fe_2SnTe_4. When black, metallic Fe_2SnTe_4 reacts with ethylenediamine (en) at 25 °C, the solid gradually turns orange, suggesting "liberation" of $SnTe_4^{4-}$. This process is accelerated by the presence of water. The generation of orange $SnTe_4^{4-}$ and of solvated Fe^{2+} ($3d^6$, high spin), i.e. of $[Fe(en)_3]_2SnTe_4$, is substantiated by the Mössbauer spectra (cf. Table 1); magnetic susceptibility measurements indicate that $[Fe(en)_3]_2SnTe_4$ is paramagnetic with magnetically noninteracting Fe^{II} centers above 5 K. The Raman spectra of both K_4SnTe_4 solutions and $[Fe(en)_3]_2SnTe_4$ display strong bands near 180 and 130 cm^{-1} (intensity ratio $\approx 1:5$), which are assigned to $SnTe_4^{4-}$ on comparison with the Raman spectra of other MX_4^{4-} species. This strongly suggests that the $SnTe_4$ tetrahedral unit is structurally intact in amorphous Fe_2SnTe_4. Thus the metallic network formed from the random, three-dimensional polymerization of Fe^{2+} and $SnTe_4^{4-}$ can be destroyed by reac-

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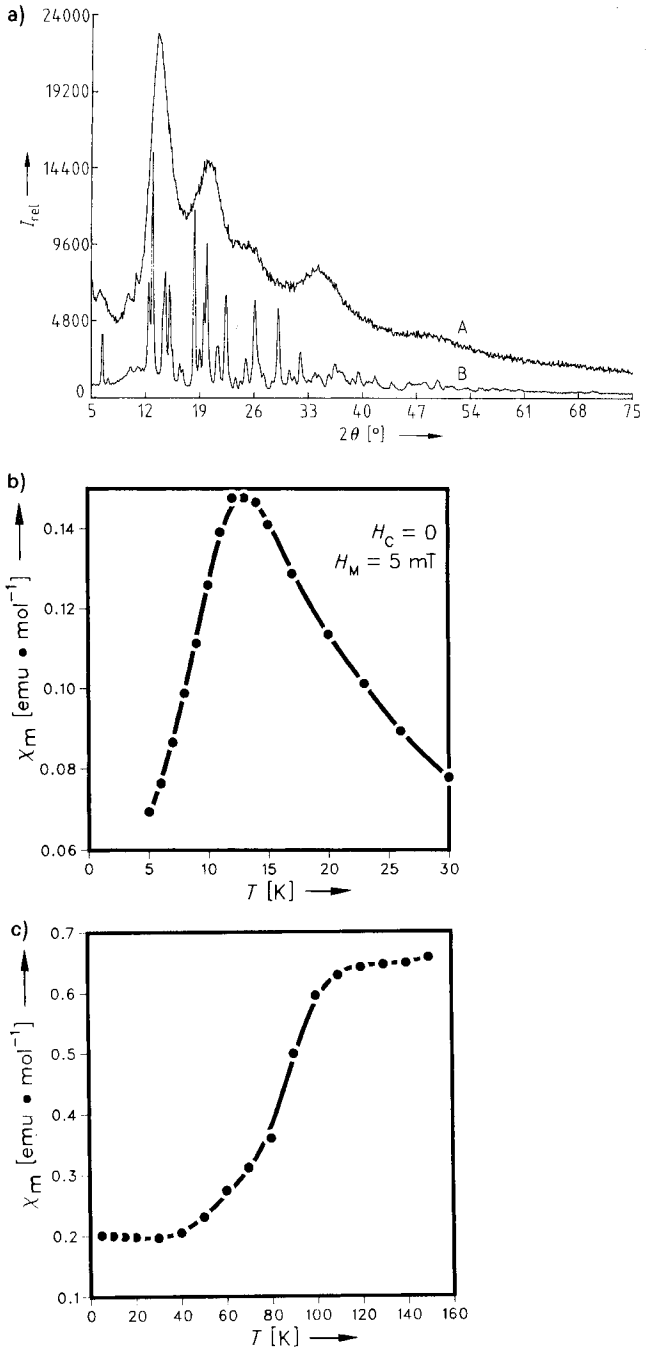

Fig. 1. a) The XRD patterns ($\lambda = 0.7107$ Å) of amorphous Fe_2SnTe_4 (curve A) and of crystalline FeTe, $FeTe_2$, SnTe obtained by heating Fe_2SnTe_4 for 24 h at 600 °C (curve B).—b) Magnetic susceptibility (direct current) of Fe_2SnTe_4 before being heated; c) after heating. Both FeTe and $FeTe_2$ are antiferromagnetic with Néel temperatures of 70 and 83 K, respectively.

tion with certain ligands leading to conversion of the solid into an insulator.

Table 1. Isomer shift (*IS*) and quadrupole splitting (*QS*) in the ^{57}Fe- and/or ^{119}Sn-Mössbauer spectra of some tellurides at 77 K (all values in mm·s^{-1} relative to Fe metal at 300 K or $CaSnO_3$ at 300 K).

Compound	^{57}Fe		^{119}Sn	
	IS	*QS*	*IS*	*QS*
K_4SnTe_4	—	—	1.71(6)	0
Fe_2SnTe_4	0.60(2)	0.48(2)	2.05(2) 3.22(4)	≈0
$[Fe(en)_3]_2SnTe_4$	1.11(2) 1.10(2)	2.32(2) 1.64(2)	1.74(7)	0
$FeTe_2$	0.57(2)	0.50(2)	—	—
SnTe	—	—	3.55(3)	0

The synthesis of amorphous metals from ionic precursors at room temperature utilizing the oxidation of main group polyanions by metal cations should provide a route to metastable materials not readily accessible by other synthetic methods, such as sputtering and thermal quenching. In principle, it should also be possible to vary the physical properties of the solids from those of an insulator (Ca_2SnTe_4) to those of a metal (Co_2SnTe_4) by controlling the amount of electron transfer from anion to cation—either by varying the relative redox potentials of the anion and cation or by incorporating reducible and nonreducible cations ($Ca_xCo_{2-x}SnTe_4$). Even in the series M_2SnTe_4 (M = Mn, Fe, Co) a transition is seen from the metallic and essentially paramagnetic Co_2SnTe_4 to Mn_2SnTe_4 having a higher resistivity and strong spin glass properties.

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Methods of Enzymatic Analysis. Volume I. Fundamentals. Edited by *H. U. Bergmeyer, J. Bergmeyer,* and *M. Grasse*. 3rd edit. Verlag Chemie, Weinheim 1983, xxiv, 574 pp., bound DM 170.00 (subscription price until June 30, 1984), thereafter DM 198.00.

For the past twenty years the first step in any enzymatic analysis has been to consult Bergmeyer. The next years will be no different: the updated and enlarged third edition of *Hans Ulrich Bergmeyer*'s "Methods of Enzymatic Analysis" has just commenced publication, and promises to play the same role as previous editions as an indispensable reference for the practicing enzymologist.

The increased interest and importance of enzymatic analysis is reflected in the size of the series: the first edition (1963) consisted of a single volume; the second edition (1974) of four volumes; the current edition is projected to comprise ten volumes. Volume 1 of this series has just appeared, and the entire series is expected to be available by 1986.

The scope of this third edition will be substantially broader than the first two editions. Considerably more background information is included, and some topics covered in the first volume in previous editions have been deferred to later volumes. The introduction—the first of three chapters for volume 1—consists of five sections covering nomenclature and units, reliability of laboratory results and practicability of procedures, standardization in enzymatic analysis, economic considerations in enzymatic analysis, and present status and future prospects for enzymatic analysis. The introduction in the previous edition emphasized the broad applicability of enzymatic analysis; the current volume assumes the reader is already convinced of the importance of the subject matter and covers general background information necessary for the broad range of currently practiced enzymatic analyses. Some specific topics *Bergmeyer* emphasizes (*Bergmeyer* is both the editor in chief of the series and the author of many individual sections in this volume) include the need for standardization of units and nomenclature in enzymology, economic considerations (interestingly, enzyme cost in most analyses is estimated to be less than 2%), and the unique advantages of enzymatic analysis (high specificity and selectivity even in complex mixtures).

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ENDOR Spectroscopy—A Promising Technique for Investigating the Structure of Organic Radicals

By Harry Kurreck*, Burkhard Kirste, and Wolfgang Lubitz

The name "ENDOR" has been known since biblical times and denotes a small town close to the Sea of Galilee (ca. 1000 B.C., 1 Sam. 28:7 ff). The acronym "ENDOR" (*E*lectron *N*uclear *DO*uble *R*esonance) characterizes the extension of electron spin resonance to electron-nuclear double resonance spectroscopy, a method that has opened up new dimensions for the investigation of complicated paramagnetic molecules. Only ENDOR spectroscopy, which has achieved technical perfection in the last decade, overcomes the resolution limitations of EPR spectroscopy, thus allowing interesting applications in the field of biochemistry. ENDOR investigations of the primary process of photosynthesis, of the mode of action of derivatives of vitamin E and K, and of the mechanism of the enzymatic catalysis of flavoenzymes in biological redox-chains have opened up new vistas. ENDOR and its extension to the triple resonance experiment TRIPLE offer, for example, the potential for a precise determination of hyperfine coupling constants, including their signs, which are frequently especially interesting. In addition to protons, a multitude of magnetic nuclei can be studied by ENDOR, such as e.g. ^{2}H, ^{13}C, and ^{14}N. The ENDOR technique is not restricted to monoradicals, but can also be applied to polyradicals in spin states of higher multiplicities (triplet, quartet, or quintet state). The experimental data accessible from ENDOR yield information about spin and charge density distributions, and about the geometries of radicals and their internal dynamics; they also provide an excellent test for the accuracy of quantum mechanical calculations.

1. Introduction— Why Electron Nuclear Double and Triple Resonance?

The chemistry of "free radicals" began in 1900 with *Gomberg*'s classical studies on the generation and chemical detection of the triphenylmethyl radical. The first electron paramagnetic resonance (EPR) experiment by *Zavoisky* in 1945[1] can be considered a milestone in the exploration of paramagnetic systems. Nowadays EPR spectroscopy has established itself as the most versatile method for investigating paramagnetic molecules. Applications extend from solid state physics, via studies of structure and dynamics of molecules, to investigations of paramagnetic intermediates in biological systems.

Due to this widespread use, the chemist should already be acquainted with the physical principles of EPR spectroscopy, the more so since the principles of magnetic resonance reveal a close relationship between EPR and the more familiar NMR spectroscopy. Similarly to NMR spectroscopy, where nuclear spin transitions between different nuclear Zeeman levels are induced, in EPR spectroscopy

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electron spin transitions between different electron Zeeman levels are stimulated. The observables in an EPR experiment are the electronic g-value, the line shape—and probably most interesting for the chemist—the hyperfine structure, from which the hyperfine interaction parameters can be extracted. By analogy to NMR spectroscopy where local structural information can be obtained from the spin-spin coupling of nuclei in different molecular positions, in EPR spectroscopy the scalar and the dipolar doupling of the unpaired electron (or of unpaired electrons) with magnetic nuclei lead to splitting of the electronic Zeeman levels into hyperfine sublevels and thus to additional EPR transitions. In contrast to NMR spectroscopy, where the spin-spin coupling is usually restricted to nuclei in small fragments of the molecule, delocalization of the unpaired electron in an organic π radical over a larger π system results in its coupling with all magnetic nuclei, producing an (integral) multispin ensemble. Even in the case of a comparatively simple organic doublet radical like triphenylmethyl with one set of three equivalent protons and two sets each of six equivalent protons, this gives rise to a thicket of (theoretically expected) $4 \times 7 \times 7 = 196$ lines. This high density of spectral lines is undoubtedly the greatest handicap of EPR spectroscopy, which makes it of limited utility in investigations of larger organic radicals because of its insufficient resolving power.

One possible way of improving the resolving power of a spectroscopic technique is offered by double resonance methods in which the sample is simultaneously irradiated with *two* resonant fields. In NMR spectroscopy different versions of such double resonance techniques are well-known. Provided the double resonance method is based on a change of level populations, e.g. in the INDOR technique, there exists a certain relationship between extended NMR techniques and the ENDOR experiment, which shall be described in detail in this article.

The *E*lectron *N*uclear *DO*uble *R*esonance (ENDOR) technique was first applied by *Feher* in 1956 to solids[2] and some time later by *Hyde* and *Maki* to organic radicals in solution[3]. This method overcomes the limited resolution of EPR spectroscopy by introducing additional selection rules. Furthermore, by detecting the NMR transitions in the microwave range, the sensitivity is enhanced by several orders of magnitude relative to pure NMR spectroscopy of radicals.

In particular, the drastically improved resolving power compared to EPR spectroscopy makes ENDOR spectroscopy highly attractive for organic chemists and biochemists. Comparison of the EPR and ENDOR spectra of the bis(biphenylylene)allyl radical illustrates this (cf. Fig. 1). Whereas only ca. 400 of the theoretically expected $5 \times 5 \times 5 \times 5 \times 2 = 1250$ lines can be resolved in the EPR spectrum, the ^{1}H-ENDOR spectrum exhibits all five possible line-pairs—one for each set of equivalent protons. The *hyperfine coupling* (HFC) constants can be extracted without difficulty and usually unambiguously without need for computer simulations. A computer simulation of the EPR spectrum with the HFC constants taken from ENDOR then yields the multiplicities. Unequivocal assignments of the HFC constants to individual molecular positions can be achieved by selective isotopic labeling.

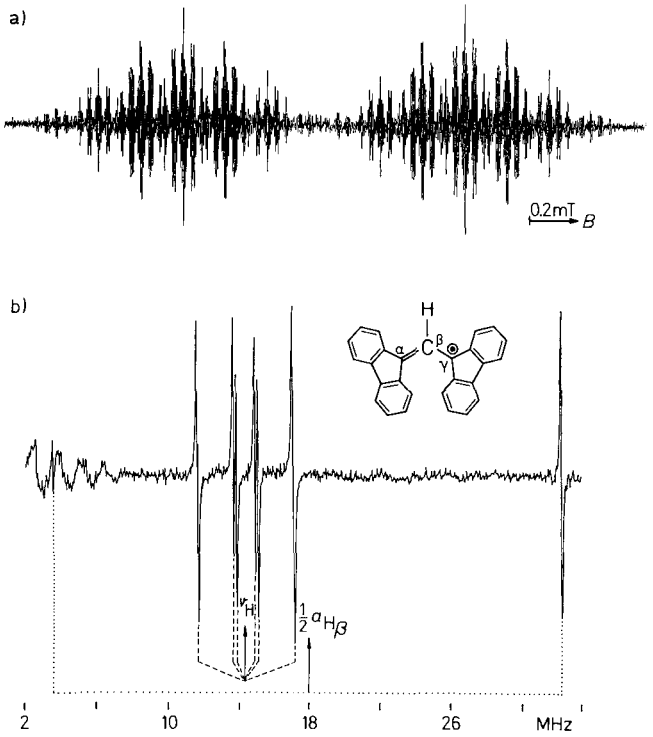


Fig. 1. a) EPR spectrum (in CCl_4, 293 K) and b) ENDOR spectrum (in mineral oil, 330 K) of the bis(biphenylylene)allyl radical. The following points should be noted: that there is a *drastic* decrease in the number of lines in the double resonance experiment (compare ENDOR/EPR); that different conditions (temperature, viscosity of the solvent) are often necessary to obtain optimum EPR and ENDOR spectra; and that the positions of the ENDOR signals—corresponding to the ENDOR resonance condition (eq. (3))—depend on the relative magnitude of the HFC constants with respect to the free nuclear frequency (ν_H); cf. [27].

The extension of ENDOR to electron-nuclear-nuclear triple resonance spectroscopy "TRIPLE" (also termed "double ENDOR"[4]) offers a further increase in resolution and sensitivity[5] and allows determination of the (relative) signs of coupling constants[6].

2. Physical Principles, Instrumentation

Excellent accounts of the theory of electron nuclear multiple resonance may be found in a series of authoritative review articles and monographs[7]. In the following, the ENDOR experiment will be described in a simple phenomenological manner.

2.1. ENDOR

In the ENDOR experiment nuclear spin transitions in paramagnetic molecules are induced by means of a suitable radio frequency (RF) field and are detected by a change in the EPR signal intensity. Figure 2 shows the energy level diagram ("four level scheme") for the simplest case of a radical with one unpaired electron ($S = 1/2$) and one magnetic nucleus ($I = 1/2$), e.g. a proton. The interaction of the electronic and nuclear spin moments with the external magnetic field gives rise to a splitting into two times two levels (Zeeman splitting), the position of which is influenced further by the hyperfine interaction between

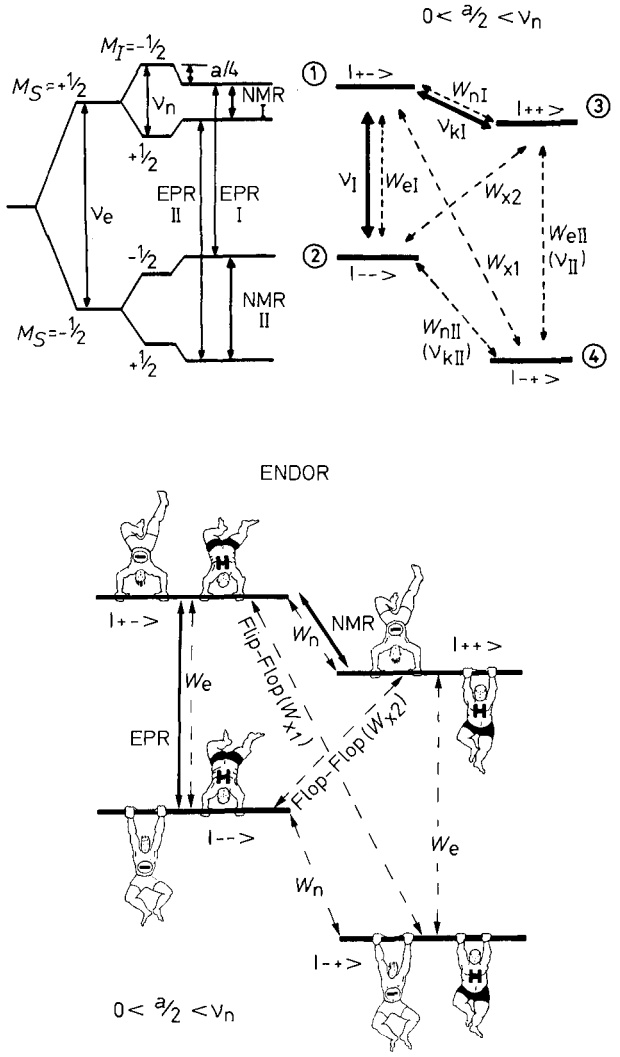


Fig. 2. Energy level diagram and "four-level scheme" for the hyperfine interaction of one unpaired electron ($S=1/2$) with one proton (or another nucleus with $I=1/2$). The solid arrows symbolize the EPR and NMR transitions induced by radiation, respectively, and the broken arrows the relaxation transitions. The bottom scheme should makes plain the "spin acrobatics" in the double resonance experiment).

electron and nucleus. The four levels are denoted by the signs of the magnetic spin quantum numbers, and the energies of the levels are given in frequency units. The solid arrows symbolize the radiation-induced electron and nuclear spin transitions, whereas the dashed arrows characterize the radiationless electron spin (W_e), nuclear spin (W_n) and cross-relaxation processes (W_{X1} and W_{X2}). In the last-mentioned process, simultaneous electron- and nuclear-spin relaxation transitions take place (cf. Section 3). With the selection rules $\Delta M_S = \pm 1$, $\Delta M_I = 0$, the two possible EPR transitions (① ↔ ②, ③ ↔ ④) arise at the frequencies

$$\nu_{EPR} = \nu_e \pm a/2 \tag{1}$$

and with the selection rules $\Delta M_I = \pm 1$, $\Delta M_S = 0$, the two NMR transitions arise at the frequencies

$$\nu_{ENDOR} = |\nu_n \pm a/2| \tag{2}$$

Equation (2) can be written in a general way as the "ENDOR resonance condition":

$$\nu_{ENDOR} = |\nu_n - a M_S| \tag{3}$$

For a monoradical with $M_S = \pm 1/2$, two signals appear in the ENDOR spectrum for each nucleus or set of equivalent nuclei, respectively, either centered about the free nuclear frequency ν_n, separated by the HFC constant a (when $|a/2| < \nu_n$ holds), or equally spaced about $a/2$, separated by $2\nu_n$ (when $|a/2| > \nu_n$ holds).

In the ENDOR experiment, an EPR transition (ν_I) is first irradiated continuously with an intensity high enough that the (spin-lattice) relaxation can no longer compete successfully with the induced rate[8]: The populations of the two levels are almost equalized, the transition is partially "saturated", and the thermal Boltzmann equilibrium distribution is perturbed.

If, additionally, an NMR transition (ν_{kI}) is also irradiated with high intensity, the total transition rate[8] ① ↔ ③ is increased, and level ① is depopulated more efficiently; the relaxation pathway is closed via a W_e (③ ↔ ④) and a W_n (④ ↔ ②) process or via a W_{X2} (③ ↔ ②) process. The desaturation of the EPR transition thus achieved gives rise to an increase in the EPR signal intensity which is recorded as the ENDOR effect. Although the ENDOR effect amounts to only a few percent of the EPR signal intensity, even under the most favorable conditions, there is a sensitivity increase of ca. 10^5 relative to that of NMR spectroscopy, resulting from the detection of the NMR transitions in the microwave frequency range (so-called "quantum transformation").

It can be shown that the magnitude of the ENDOR effect depends critically upon the relative magnitudes of the rates W_e, W_n, W_{X1}, and W_{X2}. Neglecting W_X processes, optimum ENDOR signals are obtained when W_e and W_n are comparable. Since these rates depend differently upon the so-called rotational correlation time τ_R (a measure of the Brownian rotational diffusion of molecules in solution)[9],

$$W_e \propto 1/\tau_R, \quad W_n \propto \tau_R$$

an adjustment of the relaxation rates can often be achieved by temperature variation. This can be understood in terms of the Debye-Einstein equation, which provides a connection between the effective molecular volume (V_{eff} results from the average radius of a molecule considered as a sphere), the viscosity η of the solvent, and the temperature:

$$\tau_R = V_{eff} \cdot \frac{\eta}{kT} \tag{4}$$

With decreasing temperature and increasing viscosity, W_e becomes smaller and W_n larger. The desired ratio $W_n/W_e \cong 1$ can usually be attained through temperature/viscosity optimization of the solution. Since for protons W_n is normally much smaller than W_e, optimum ENDOR signals in solvents of low viscosity such as toluene, tetrahydrofu-

ran (THF) or 1,2-dimethoxyethane (DME) are obtained near the respective freezing points of the solutions.

In summary, fulfillment of the following conditions are necessary for a successful ENDOR experiment:

- (a) An EPR transition and
- (b) an NMR transition have to be saturated; the required microwave and radio frequency powers increase with increasing relaxation rates[10].
- (c) The relaxation rates W_e and W_n have to be of comparable magnitude, or cross-relaxation processes must be effective.
- (d) Finally, it should be emphasized that the quality of the sample (concentration, absence of oxygen) is of crucial importance.

The simplification of the spectra achievable by ENDOR will be illustrated using the hyperfine energy level diagram of the *p*-benzosemiquinone radical anion or, more generally, a radical with one unpaired electron and four equivalent protons (cf. Fig. 3). Whereas the EPR spectrum consists of a quintet of signals with binomial intensity distribution (1:4:6:4:1), the ENDOR spectrum exhibits only two signals. Generally speaking, in EPR spectroscopy the number of signals increases *multiplicatively* with the number of nonequivalent nuclei, whereas in the ENDOR experiment the increase is only *additive*. In a monoradical, each set of equivalent magnetic nuclei gives rise to just *one* ENDOR line-pair, irrespective of the number of nuclei per set.

Figure 4 shows, among others, the EPR and ENDOR spectra of the phenalenyl radical, which contains one set of three and a set of six equivalent protons. Correspondingly, the EPR spectrum consists of $4 \times 7 = 28$ signals and the ENDOR spectrum only of four signals. A more complicated example demonstrating the resolution enhancement of ENDOR more convincingly has already been shown in Figure 1.

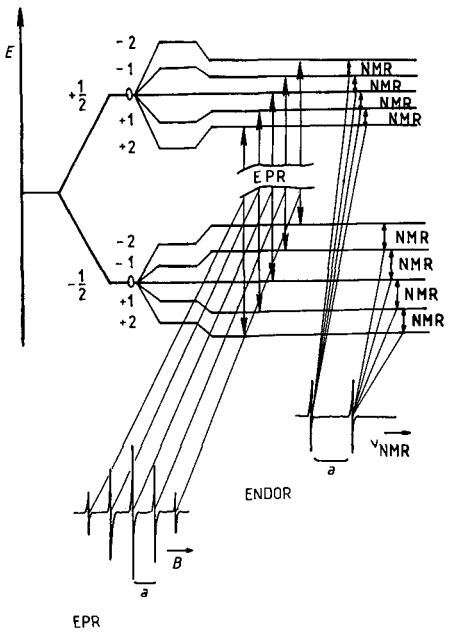


Fig. 3. Energy level diagram of a hyperfine-coupled spin system consisting of one unpaired electron ($S = 1/2$) and four equivalent nuclei ($I = 1/2$).

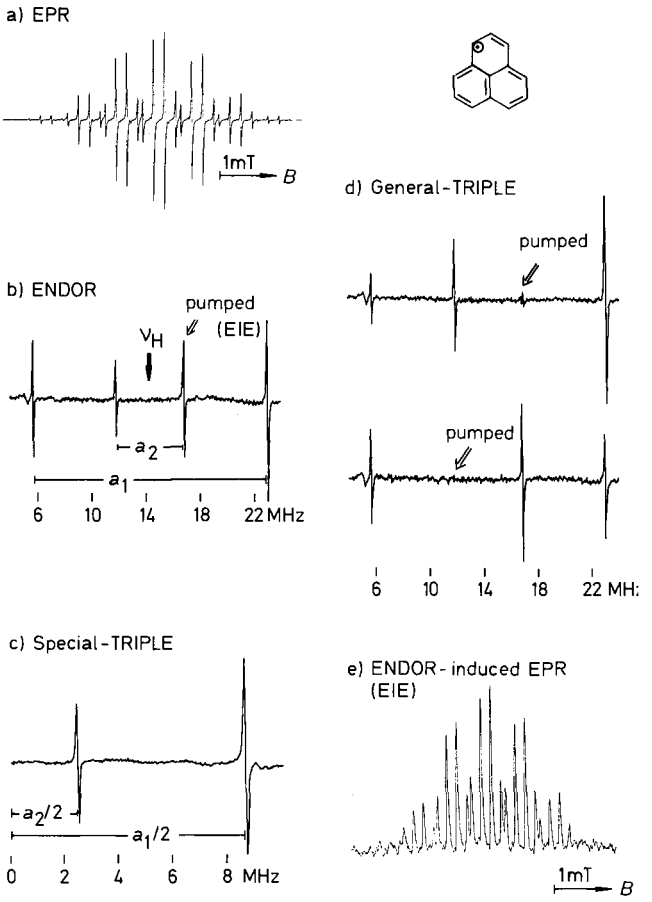


Fig. 4. Spectra of the phenalenyl radical (in mineral oil, 300 K), obtained by application of the magnetic resonance techniques EPR, ENDOR, special TRIPLE, general TRIPLE, and ENDOR-induced EPR (EIE): ENDOR increases the resolution relative to EPR; special TRIPLE resonance extends the range of applicability (temperature, solvent); general TRIPLE resonance yields the signs of the HFC constants; and ENDOR-induced EPR enables the spectra of different radical species in a sample to be recorded selectively.

Whereas the multiplicity, i.e. the number of equivalent nuclei belonging to each set, is reflected in the intensity distribution of a resolved EPR spectrum, this information is lost in an ENDOR spectrum. The reason for this is easily understood, since the ENDOR signal intensity is essentially determined by the individual relaxation properties of the particular nuclei in the respective molecular positions. A systematic decrease of the ENDOR signal intensities is found for small hyperfine couplings[11]. Thus the assignment of individual ENDOR signals to particular molecular positions is more difficult. Moreover, the high-frequency component of an ENDOR line-pair is often more intense than the low-frequency one at the same RF power. This so-called "hyperfine-enhancement effect"[12] becomes more pronounced as the frequency difference between the two components increases. For example, in Figure 1 the high-frequency ENDOR signal (at ca. 33 MHz) is much more intense than the respective low-frequency one and, furthermore, this signal of the single central proton is of the same intensity as the ENDOR lines belonging to the sets of four equivalent protons in the fluorenylidene moieties. The number of equivalent nuclei belonging to a particular HFC constant can be determined by computer simulation of a sufficiently resolved EPR spectrum with the coupling con-

stants obtained from ENDOR. The unequivocal assignment to particular molecular positions is performed by specific isotopic labeling; however, this usually requires considerable preparative effort. Figure 5 illustrates the unequivocal assignment of ENDOR signals by this method using several *m*-terphenyl radical anions[13]. The arrows in the figure indicate the positions of resonance lines in the ^{1}H-ENDOR spectrum that disappear upon deuteration.

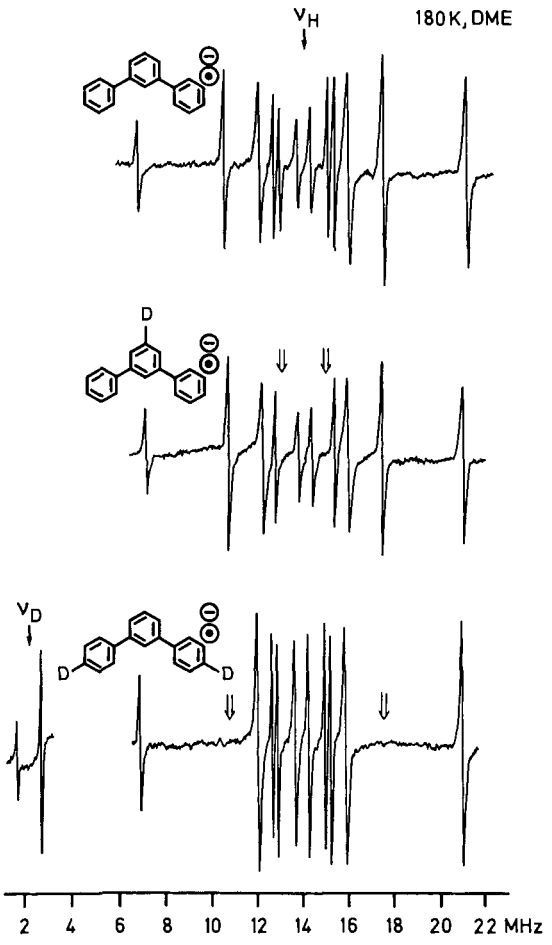


Fig. 5. ^{1}H- and ^{2}H-ENDOR spectra of *m*-terphenyl radical anions. In the spectra of the selectively 5′- or 4,4″-deuterated compounds the respective line pair (marked by arrows) disappears, thus allowing an *unequivocal* assignment of the corresponding HFC constants to these positions in the molecule [13].

2.2. Special TRIPLE Resonance

In Section 2.1 it was demonstrated (Figure 2) that the ENDOR effect can be interpreted as arising from a "short circuit" of a nuclear spin transition. Clearly, this effect should be enhanced substantially if *both* relaxation "resistances" W_{nI} and W_{nII} could be short-circuited simultaneously by means of an additional NMR frequency[5a]. The experimental realization of TRIPLE resonance experiments on organic radicals in solution was first achieved by *Möbius, Biehl, Dinse,* and *Plato*–a group which has played a leading role in the development of ENDOR spectroscopy—in 1974 (special TRIPLE)[5b] and 1975 (general TRIPLE)[6].

In the special TRIPLE experiment the sample is irradiated with *two* RF fields in addition to the "saturating" microwave radiation. By generating side bands around the free nuclear frequency, one RF field is swept to higher, the other to lower, frequencies and thus *both* NMR transitions of each set of equivalent nuclei are always "hit" *simultaneously*. Figure 4c shows that each hyperfine coupling gives rise to just *one* special TRIPLE signal, which appears separated from the origin of the NMR frequency axis ($\nu_{NMR}=0$) by the frequency $|a/2|$. The advantages offered by the special TRIPLE version compared to ENDOR are:

- (a) Enhancement of sensitivity (improved signal-to-noise ratio).
- (b) Improved resolution, as can be shown experimentally and theoretically[5,7c].
- (c) Under favorable experimental conditions (induced rate of nuclear spins $\gg W_e \gg W_n$), the signal intensities reflect the ratio of numbers of equivalent nuclei per set—as in NMR of diamagnetic compounds—because the desaturation of EPR transitions is not primarily determined by the nuclear spin relaxation rate W_n, in contrast to ENDOR.
- (d) This fact (c) also leads to a significantly smaller temperature dependence of the special TRIPLE signal intensity, so that e.g. biological systems can be investigated under (physiological) conditions which do not lend themselves to a measurable ENDOR effect.

The special TRIPLE experiment can be applied in the same way, even to those hyperfine-coupled nuclei for which $|a/2|>\nu_n$ is valid (see Section 2.1), since "negative" frequencies are reflected at the origin. For several reasons (second-order frequency shifts, high relaxation rates W_n), however, in this situation special TRIPLE usually offers no advantage relative to ENDOR experiments.

2.3. General TRIPLE Resonance

Besides pure π conjugation, the different mechanisms of spin density transfer (such as π-π, and π-σ spin polarization or hyperconjugation) can give rise to *positive* as well as *negative* spin densities at the nucleus, and thus via hyperfine coupling to HFC constants with *positive* or *negative* signs, respectively. It is therefore of great interest to be able to determine both the signs of HFC constants *and* their magnitudes. The general TRIPLE technique offers the potential of a simple, elegant and unambiguous method for the determination of the relative signs of HFC constants. In contrast, the applicability of other methods for determination of signs is limited, e.g. wide-line NMR spectroscopy (NMR measurement of the Fermi contact shift) of organic radicals[14] or EPR spectroscopy in liquid crystals (direction of the hyperfine shift on passing from the isotropic to the nematic phase)[15].

In contrast to special TRIPLE, NMR transitions of *different* sets of nuclei of the same kind or of different kinds are saturated *simultaneously* in the general TRIPLE experiment. In practice, one EPR component is saturated, and an

NMR transition is "pumped" with the first (unmodulated) NMR frequency. The whole range of NMR resonances is scanned with the second (modulated) RF field. The additional pumping frequency gives rise to characteristic intensity changes of the signals compared to those of the ENDOR spectrum, and allows the determination of the relative signs of the HFC constants (see Fig. 4d). If, for example, the high-frequency component of the smaller coupling of the phenalenyl radical is pumped (marked by an arrow in Fig. 4d, top), the intensity of the respective *low-frequency* signal increases because this corresponds to a *special* TRIPLE experiment. On the other hand, the *high-frequency* component of the large coupling is enhanced, and the low-frequency component on the other side—with respect to the free proton frequency ν_H—decreases in intensity. This phenomenon allows it to be concluded that the two HFC constants have *opposite signs*. If the corresponding experiment is performed with the pumping frequency set on the low-frequency ENDOR line of the small coupling, these intensity relations are reversed (Fig. 4d (bottom)). This analysis of general TRIPLE spectra is only valid, however, if the gyromagnetic ratios of the nuclei under consideration have the same sign.

In a heteronuclear general TRIPLE experiment between, e.g., ^1H and ^{29}Si[16] or ^1H and ^{15}N[17], these intensity rules have to be reversed. Since this method deals with the determination of *relative* signs, an interpretation of this effect requires at least an eight-level scheme with two different nuclei ($I = 1/2$; $a_1 \neq a_2$). Figure 6 shows such diagrams for equal (left diagram) or opposite signs (right) of the two HFC constants. In both cases ν_2^- denotes the pumping frequency, and ν_1^- and ν_1^+ the monitoring frequencies. An increase in intensity is to be expected if the pumping and monitoring frequencies belong to *different* M_S manifolds. A closer inspection of Figure 6 reveals that only in this situation can a "relaxation loop" be formed which consists exclusively of W_e processes and short-circuited W_n processes; hence, no "bottleneck" W_n is involved. If pumping and monitoring frequencies are irradiated in the same M_S manifold, however, the relaxation loop can only be closed by including W_n processes; the signal intensity is then even smaller than in an ENDOR experiment ("bypass"). Large TRIPLE effects occur if $W_e \gg W_n$, i.e. *outside* the optimum ENDOR range ($W_e \cong W_n$). If the signs of the two HFC constants are the same (in Figure 6 left, positive), *both* low-frequency components ν_2^- and ν_1^- belong to the same M_S manifold. The right-hand diagram in Figure 6 describes, e.g., the TRIPLE experiment on the phenalenyl radical depicted in Figure 4: The HFC constants have opposite signs, and consequently the two low-frequency NMR transitions belong to *different* M_S manifolds. In this case, the ENDOR signal is enhanced if pumping and monitoring frequencies are situated on the same side of ν_H.

In addition to determination of signs, an increase in resolution can occasionally be achieved using the general TRIPLE technique, provided two HFC constants have similar absolute values but opposite signs: The pumping frequency enhances the signal of one set of nuclei but weakens that of the other, thus giving rise to a small shift in the resonance position of the superposed signals. A shift in the opposite direction is achieved by appropriate

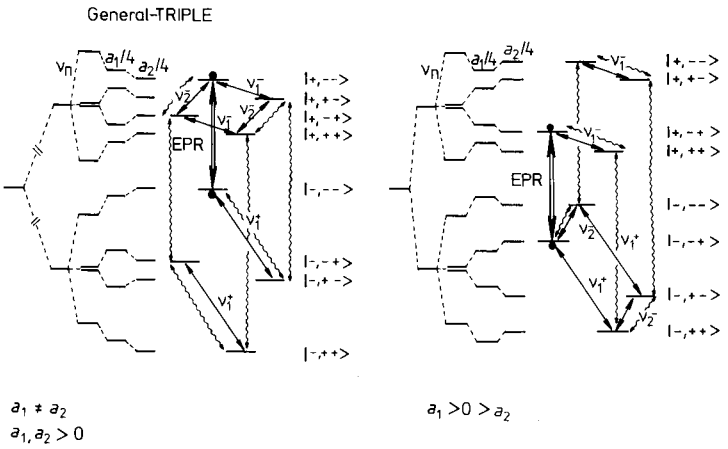


Fig. 6. Energy level diagrams for the hyperfine interaction of one unpaired electron ($S = 1/2$) with two different protons (or two other nuclei with $I = 1/2$) for clarification of the general TRIPLE effect. The HFC constants in the left diagram have the same (positive) signs and in the right one, opposite signs: ν_2^- denotes the NMR pumping frequency, and ν_1^- and ν_1^+ the NMR scan frequencies. *Left:* A closed relaxation loop between the two hyperfine levels of the pumped EPR transition $|-,--> \leftrightarrow |+,-->$ consisting exclusively of W_e and short-circuited W_n processes can *only* occur if ν_1^+ is irradiated. *Right:* For $a_1 > 0 > a_2$ such a relaxation loop—again symbolized by the sinuous line—exists only if ν_1^- is irradiated.

switching of the pumping frequency[13]. Coincident ENDOR signals of HFC constants with opposite signs and equal number of nuclei can be recognized since these lines do not "react" on the TRIPLE effect when the pumping frequency is changed to another NMR transition, i.e. their intensity remains unaltered.

2.4. ENDOR-Induced Electron Paramagnetic Resonance (EIE)

In the chemistry of organic free radicals, it happens occasionally that more than one radical is formed at the same time. Whereas the EPR spectrum of such a mixture—especially when the g-values are similar—often consists of a superposition of the contributing spectra which is difficult to analyze, the individual EPR spectra can be recorded separately using the interesting variant "ENDOR-induced EPR" (EIE), provided separate signals for the different radicals appear in the ENDOR spectrum[18a]. The EIE experiment is illustrated in Figure 4 for the phenalenyl radical: While the NMR frequency is positioned at an ENDOR line (Fig. 4b), the external magnetic field is swept over the range of EPR absorptions, and gives rise to the ENDOR-induced EPR spectrum of phenalenyl depicted in Figure 4e, which, for experimental reasons, has the appearance of an absorption spectrum. The following example serves to illustrate how the EIE technique allows individual species to be selectively studied in a mixture of different radicals: We recently had to decide[18b] whether the ENDOR spectrum of a partially deuterated phenalenyl radical (Fig. 7) could be assigned to a species with H atoms in positions 1 *and* 2, or whether the solution consisted of a mixture of species with only *one* H atom in position 1 *or* 2 (the intensities of the ENDOR signals were ignored). The EIE spectrum gave the unequivocal answer: Depending on the setting of the NMR pumping frequency (Ⓐ or Ⓑ), different EIE spectra (Ⓐ and Ⓑ) were obtained. The solution

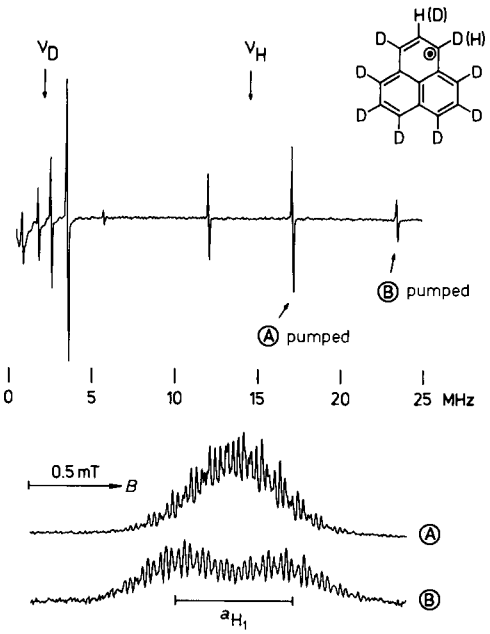


Fig. 7. ENDOR (top) and ENDOR-induced EPR spectra (bottom) of phenalenyl radicals with the same degree of deuteration but different distribution of the isotopes: The EIE spectrum Ⓐ obtained with the NMR pumping frequency set on the high-frequency ENDOR component of the small coupling arises from radicals with the hydrogen atom in position 2; analogously the EIE experiment Ⓑ indicates the presence of phenalenyl radicals with a hydrogen atom in position 1. Furthermore, it can be deduced from the relative intensities of the ENDOR signals that the concentration of the [2-^{1}H] species is larger than that of the [1-^{1}H] species (cf. [18b]).

therefore consisted of a mixture of phenalenyl radicals in which eight of the nine possible positions are always deuterated, with the H atom in either position 1 or 2.

It is worth mentioning that the signal intensity can be increased significantly by using the version "TRIPLE-induced EPR"[19]. In principle, such a selection experiment is also possible using a general TRIPLE experiment. If an ENDOR spectrum exhibits signals from different radicals, of course, only those ENDOR components "react" to the additional pumping frequency which belong to the same level scheme, i.e. to the same radical, as the pumped component.

2.5. Instrumentation and Sample Preparation

Figure 8 shows the block diagram of the spectrometer used in the authors' laboratory. The spectrometer is capable of recording EPR, ENDOR, ENDOR-induced EPR, as well as special and general TRIPLE resonance spectra. The components of the commercial EPR spectrometer (Bruker ER 220 D) are enclosed by the broken lines. The basic features of the broad-band NMR channel have been described previously[7c, 7f, 20].

Sample preparation using the various methods of generating radicals by chemical, electrolytic, and photolytic means is accomplished essentially according to the relevant methods used in EPR spectroscopy[23]. Only a limited number of solvents are suitable for ENDOR spectroscopy; however, those solvents which form a glass on cooling (toluene, ethanol, 2-methyltetrahydrofuran) have proved particularly useful, because the high viscosity thus achievable frequently allows the condition $W_e \simeq W_n$ to be adjusted.

3. Further Nuclei Accessible to ENDOR (ENDOR of Nuclei other than Protons)[25]

Until 1970, ENDOR spectroscopy in solution was applied exclusively to study the protons within the radicals, which are particularly suited for this technique: The mag-

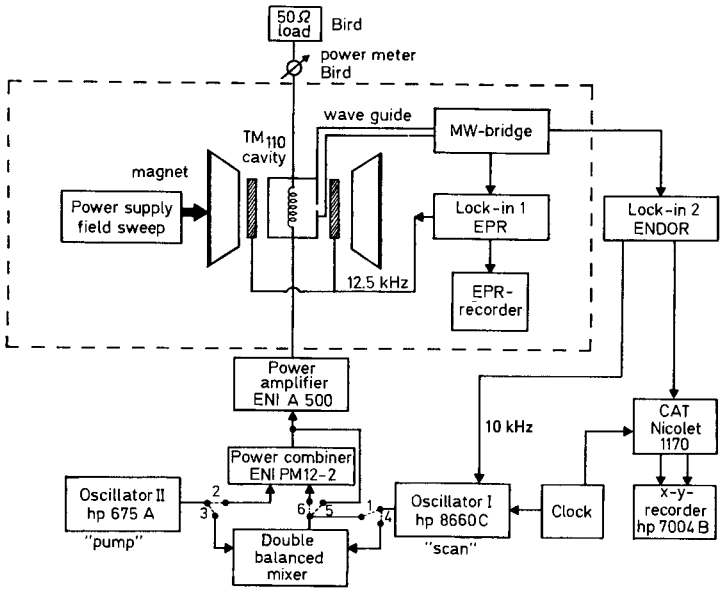


Fig. 8. Block diagram of an ENDOR/TRIPLE spectrometer. The dashed line encloses the EPR spectrometer. For very elaborate EPR measurements (sensitivity, resolution), the ENDOR cavity should be replaced by an EPR cavity. The different modes of operation require the following connections, denoted by 1—6: ENDOR: 1, 5 closed; 2, 3, 4, 6 open. General TRIPLE: 1, 2, 6 closed; 3, 4, 5 open. Special TRIPLE: 3, 4, 5 closed; 1, 2, 6 open. The MW and RF fields are generated by means of a Bruker ENDOR cavity (ER 200 ENB) of TM_{110} type with internal NMR coil, which may have different numbers of turns, and is fixed to a double-walled quartz Dewar. 12.5 kHz field modulation is used for recording the EPR spectra in the field sweep method (Hall probe stabilization). The EPR signals are plotted on the recorder of the Bruker console after phase-sensitive rectification and amplification (lock-in 1). For recording ENDOR spectra, the spectrometer is adjusted to the absorption maximum of the selected EPR line by means of a field frequency lock (Bruker ER 033), and the field modulation is switched off. The frequency generator I (hp 8660 C) generates the 10 kHz frequency-modulated NMR frequency. This is amplified (ENI A 500), passed through the NMR coil in the cavity, and dissipated in a 50 Ω load (Bird 8201) after its power has been measured (Bird Wattmeter 43). The change in the EPR absorption of the sample caused by the NMR transitions undergoes phase-sensitive rectification, is amplified (lock-in 2, Ithaco 393) and stored in a spectrum accumulator (Nicolet 1170). The channel advance of the CAT is synchronized with the change in the oscillator frequency (I) via a clock. The ENDOR signals in the first derivative mode can be plotted versus the NMR frequency on an x,y recorder (hp 7004 B). For performing general TRIPLE experiments, the unmodulated NMR frequency of an ENDOR signal is also irradiated (see Section 2.3). This frequency is generated by oscillator II (hp 675 A) and added to the first (swept, frequency-modulated) NMR frequency using a combiner (ENI PM 12-2). In the special TRIPLE experiment the double balanced mixer (Industrial Electronics SRA-3H) produces two frequency-modulated side bands at ν_{II} (from oscillator II) $\pm \nu_I$ (from oscillator I). Provided the carrier frequency ν_{II} corresponds to the Larmor frequency of one type of nuclei in the radical, the high- and the low-frequency ENDOR transitions for all HFC constants of these nuclei are always irradiated *simultaneously*; this procedure can even be used if $|a/2| > \nu_n$, with the only proviso that the range $\nu_I \cong \nu_{II}$ ($|a/2| = \nu_n$) should be avoided (see Section 2.2). The temperature of the sample is usually adjusted by means of a flow of nitrogen gas (e.g. temperature control unit Bruker VT-1000), but a helium cryostat may be used instead [21]. Slotted cavities allow light irradiation of the sample in situ [7f, 22a, b]. Computerized ENDOR spectrometers are also available; the computer is used, inter alia, to control the field position, the scan oscillator, and the RF power, in addition to data acquisition, and handling and storage of the spectra [7f, 22c].

netic moment of the hydrogen nucleus is relatively large, and therefore the resonant frequency ν_H of the free proton (the "free proton frequency") is situated in an experimentally easily accessible range (13—15 MHz, in the field range of an X-band EPR spectrometer); the π-σ spin polarization mechanism which is operative through the C—H σ bond gives rise to pure s spin density in the proximity of the protons and thus to a comparatively small hyperfine anisotropy; relatively small RF powers are consequently sufficient to saturate the NMR transitions. It was of great interest both for theoretical and applied ENDOR spectroscopy to extend this method to further nuclei such as ^2H, ^{13}C, $^{14,15}N$, and ^{19}F for example, the hyperfine coupling of a ^{13}C nucleus within the π system is expected to be much more sensitive toward changes in the geometry than those of peripheral protons. Finally, all nuclei in the π skeleton not connected to protons are "blind" for purposes of ^1H-ENDOR spectroscopy.

Table 1. Properties of magnetic nuclei from which ENDOR-in-solution signals have been obtained so far, see text (^2H- and ^{15}N-ENDOR spectroscopy were only possible with isotopically enriched radicals.)

Nucleus	Nuclear spin I	Free nuclear frequency [MHz] (B_0=328.8 mT)	Magnetic moment μ_I (in μ_n)	Natural abundance [%]
^1H	1/2	14.00	2.7927	99.99
^2H	1	2.15	0.8574	0.015
^7Li	3/2	5.44	3.2560	92.58
^{10}B	3	1.50	1.8007	19.78
^{11}B	3/2	4.49	2.6880	80.22
^{13}C	1/2	3.52	0.7022	1.11
^{14}N	1	1.01	0.4035	99.63
^{15}N	1/2	1.42	−0.2830	0.37
^{19}F	1/2	13.17	2.6273	100
^{23}Na	3/2	3.70	2.2161	100
^{27}Al	5/2	3.65	3.6385	100
^{29}Si	1/2	2.78	−0.5548	4.70
^{31}P	1/2	5.67	1.1305	100
^{39}K	3/2	0.65	0.3910	93.10
^{85}Rb	5/2	1.35	1.3482	72.15
^{87}Rb	3/2	4.58	2.7414	27.85
^{117}Sn	1/2	4.58	−0.9132	7.61
^{119}Sn	1/2	4.99	−0.9949	8.58
^{133}Cs	7/2	1.84	2.5642	100
^{203}Tl	1/2	8.00	1.5960	29.50
^{205}Tl	1/2	8.08	1.6116	70.50

However, "non-proton" ENDOR spectroscopy faces far greater experimental difficulties than ^1H-ENDOR spectroscopy. Thus, magnetic nuclei occurring in low natural abundance such as ^2H, ^{13}C, and ^{15}N require isotopic labeling[26]. The generally smaller magnetic moment and the lower free nuclear frequency of nuclei other than protons can cause experimental problems (as long as $|a/2| < \nu_n$). Large π spin populations at magnetic nuclei, e.g. at ^{13}C atoms located in the skeleton of aromatic rings, give rise to large hyperfine anisotropies and in the case of heteroatoms (nitrogen, oxygen, halogens) often to large g-value anisotropies. These quantities strongly influence the nuclear- and electron-spin relaxation rates[7d]. In addition, the experimental difficulties of the ENDOR technique increase considerably if high microwave (> 100 mW) and RF powers (> 200 W) are required, in particular, simultaneously. However, nowadays substantial technological improvements allow ENDOR spectroscopy to be performed on a whole series of "non-proton" nuclei (cf. Table 1).

Figure 9 shows the multinuclear EPR and ENDOR spectra of a perdeuterated—except for the proton at the β-carbon atom—and 90% β-^{13}C labeled bis(biphenylylene)allyl radical. Comparison of the EPR spectra in Figures 9 and 1 reveals a drastic decrease in spectral resolution, caused firstly by the smaller gyromagnetic ratio of deuterium (1/6th that of a proton), secondly by its larger spin quantum number ($I_D = 1$, $I_H = 1/2$), and thirdly by enlarged line widths arising from the ^{13}C hyperfine anisotropy. The ENDOR spectrum, optimized for three different kinds of nuclei, however, is completely resolved. The ^2H-ENDOR lines are centered about the free deuterium frequency $\nu_D(|a/2| < \nu_D)$, whereas the ^1H- and ^{13}C-ENDOR signals are equally spaced at about half the respective HFC constant, separated by twice the free nuclear frequency ν_H or $\nu_{^{13}C}$ ($|a/2| > \nu_n$).

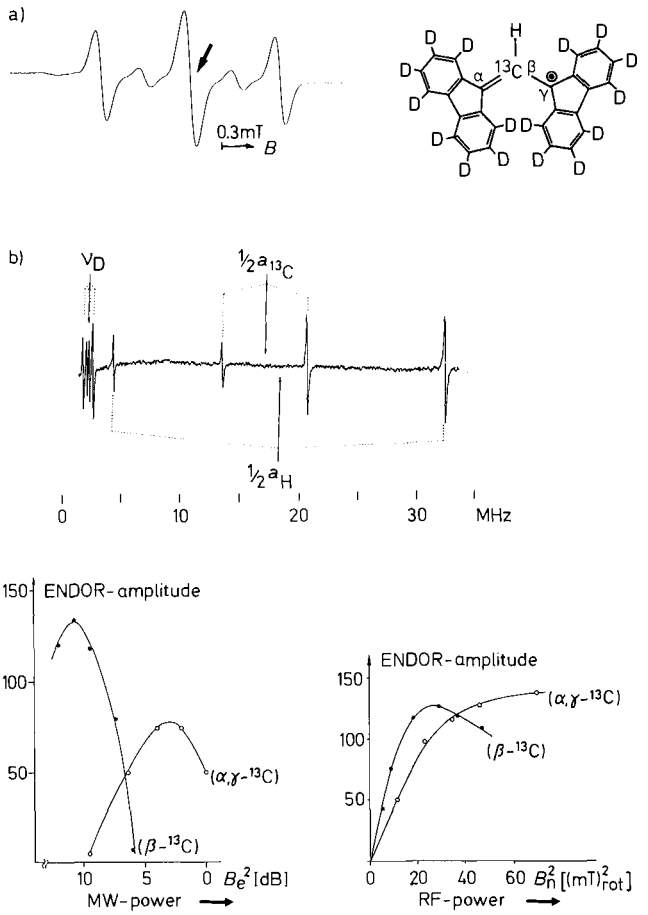


Fig. 9. Multinuclear a) EPR and b) ENDOR spectra (in mineral oil, 360 K) of the selectively deuterated and ^{13}C-labeled bis(biphenylylene)allyl radical. The arrow in the EPR spectrum denotes the field setting for the ENDOR experiment. Note that the experimental conditions were not changed to record the ENDOR spectrum. On the bottom left is plotted the dependence of the signal amplitudes of the high-frequency ^1H-ENDOR signals of the β- and α,γ-labeled compounds, respectively, on the microwave power. On the bottom right, the signal amplitude of the high-frequency ^{13}C-ENDOR lines of these radicals is shown as a function of the radio frequency power. In both cases the α,γ-^{13}C labeled compound requires higher powers to achieve an optimum ENDOR effect because of the larger hyperfine anisotropy (cf. [27]).

The ^{13}C isotope, which is particularly interesting for the organic chemist, will be discussed first. The ^{13}C nucleus in the β-position of the bis(biphenylylene)allyl radical behaves typically in terms of the optimum ENDOR effect, i.e. somewhat higher microwave and RF powers are required compared to those used for the ^{1}H-ENDOR spectrum of the unlabeled compound (Fig. 9). The α- and γ-positions of this molecule exhibit much larger spin populations than the β-position. As expected, ^{13}C-ENDOR spectroscopy requires markedly larger powers and the use of higher temperatures because of the larger hyperfine anisotropy at these positions. Figure 9 (bottom left) shows the dependence of the ENDOR signal amplitudes of the high-frequency proton lines of the two differently labeled molecules on the microwave power; whereas on the bottom right the intensities of the high-frequency ^{13}C-ENDOR signals are depicted as a function of the RF power[27].

Another instructive example is offered by the ^{13}C-ENDOR investigation of ^{13}C-labeled galvinoxyls ("*Coppinger*'s radical")[28]. Whereas the unsubstituted, selectively deuterated and ^{13}C-labeled galvinoxyl radical again exhibits the typical ENDOR behavior, i.e. ^{13}C-ENDOR requires higher temperatures and larger microwave and RF powers compared to ^{1}H- and ^{2}H-ENDOR, the result obtained for the *tert*-butyl substituted and ^{13}C-labeled galvinoxyl radical was completely unexpected (cf. Fig. 10): The optimum ^{13}C-ENDOR intensities are obtained at comparatively low temperatures and powers. Moreover, the low-frequency ^{13}C-ENDOR signal can even be detected in the *unlabeled* molecule, i.e. in natural abundance (1.1%). This signal is also shown in Figure 10 (middle, right). (The high-frequency component, which is certainly more intense because of the "hyperfine enhancement", coincides accidentally with a ^{1}H-ENDOR signal.) Clearly this basically different relaxation behavior of the two ^{13}C nuclei means that the *tert*-butylgalvinoxyl radical, in contrast to many other substituted compounds of this type, no longer behaves like a "genuine" galvinoxyl radical with a completely delocalized π system comprising two equivalent aryl rings. Owing to the *different* twist angles of the rings it has to be described as an equilibrating substituted phenoxyl radical.

This interpretation is confirmed by the investigation of 4-benzoyl-2,6-di-*tert*-butylphenoxyl radical ^{13}C-labeled at the carbonyl carbon which also exhibits such unusual ^{13}C-ENDOR behavior[29]. A natural abundance ^{13}C-ENDOR signal was observed in this radical for the first time. HMO-McLachlan and INDO calculations yielded a very low p_z-spin population at the carbonyl C atom. The ^{13}C hyperfine anisotropy is therefore extremely small in this system, and could be confirmed experimentally by ENDOR investigations in liquid crystals (see Section 4). The ^{13}C hyperfine coupling results almost exclusively from π-σ spin polarization, and the relaxation properties of the ^{13}C nucleus correspond to those of the protons, in full agreement with the experimental observation[30].

The successful detection of a nuclear resonance of ^{13}C in natural abundance by ENDOR spectroscopy testifies convincingly the increase in sensitivity relative to NMR, achievable through quantum transformation. Recently it

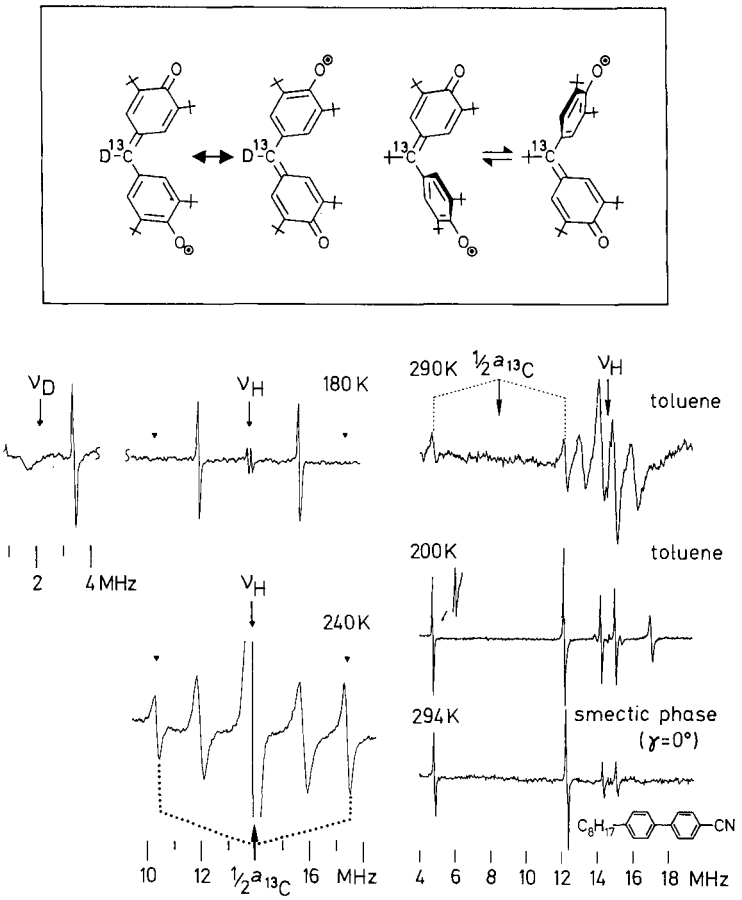


Fig. 10. ^{1}H-, ^{2}H-, and ^{13}C-ENDOR spectra of galvinoxyls. The formulas at the top illustrate that introduction of a bulky substituent converts the galvinoxyl with equivalent aryl rings and a completely delocalized π system into an equilibrating phenoxyl radical with differently twisted aryl rings. Galvinoxyl exhibits typical ^{13}C-ENDOR behavior (bottom left), whereas in the *tert*-butyl compound ^{13}C-ENDOR signals are also obtained at lower temperatures (200 K) or in solvents of high viscosity (smectic phase of a liquid crystal). It is especially noteworthy that the *tert*-butylgalvinoxyl exhibits ^{13}C-ENDOR resonances even in *unlabeled* radicals, i.e. in natural abundance: see the signal at 5 MHz in the ENDOR spectrum at 200 K (middle right) (cf. [28]).

was shown that whole sets of ^{13}C HFC constants could be determined by ^{13}C-ENDOR experiments on unlabeled radicals, provided these are extensively deuterated[31].

In ENDOR investigations of ^{13}C-labeled radicals with a large p_z-spin population, and hence large hyperfine anisotropy, pronounced intensity differences of the ^{13}C-ENDOR line pairs are frequently observed, and it depends on the setting of the external magnetic field in the EPR spectrum whether the high- or the low-frequency ENDOR component is more intense. This effect cannot be accounted for solely in terms of the "hyperfine enhancement" mentioned in Section 2.1, but rather has to be ascribed to so-called "cross-relaxation processes". As can be seen from Figure 2, electron- and nuclear-spin can flip simultaneously. The transition $|+->\leftrightarrow|-+>$ (flip, flop) is denoted W_{X1}, whereas W_{X2} symbolizes the process $|++>\leftrightarrow|-->$ (flop, flop). Evidently the condition $W_e \cong W_n$ for optimum ENDOR signals is no longer valid when W_X processes are efficient ($W_X > W_n$), since a closed "relaxation loop" arises from saturation of *one* NMR transition. Cross-relaxation processes are of importance, espe-

cially at elevated temperatures and large hyperfine anisotropies ($W_{X2} > W_{X1}$) or for time-modulated isotropic HFC constants ($W_{X1} > W_{X2}$)[18b,32]. In Figure 11 the situation is illustrated using the corresponding energy level diagrams for the perdeuterated triphenylmethyl radical which is ^{13}C-labeled to 90% at the central C atom[33]. If, for example, the low-field EPR component is saturated, the high-frequency signal in the ^{13}C-ENDOR spectrum is more intense (case Ⓐ), whereas positioning the external magnetic field at the high-field ESR signal gives rise to an ENDOR spectrum with a more intense low-frequency signal, case Ⓑ. Thus, a W_{X2} process dominates in this system, arising from the large ^{13}C hyperfine anisotropy.

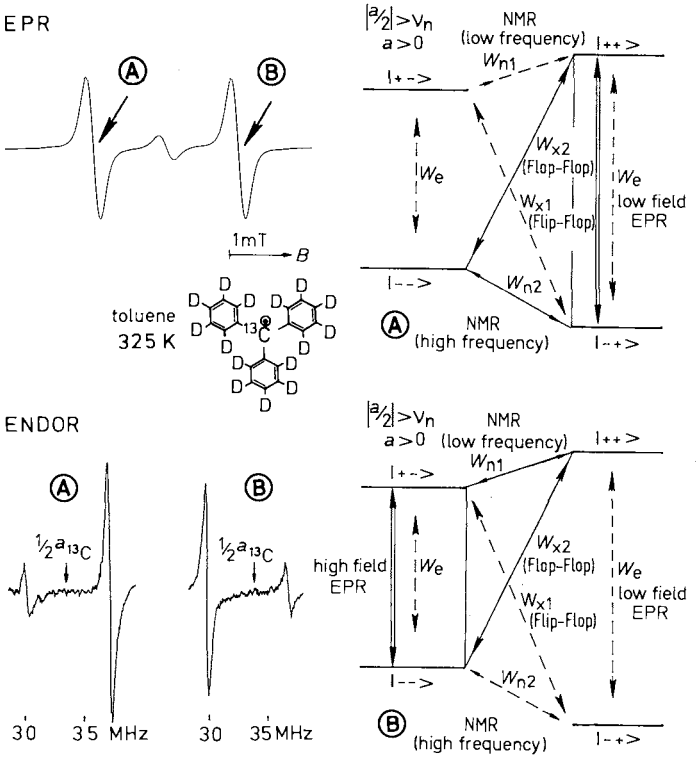


Fig. 11. EPR and ENDOR spectra of the ^{13}C labeled and perdeuterated triphenylmethyl radical. The large ^{13}C hyperfine anisotropy gives rise to a dominant W_{X2} process, so that a closed relaxation loop without inclusion of W_{n1} is obtained with the low-field setting in the EPR spectrum Ⓐ, whereas the NMR transition W_{n2} is avoided with the high-field setting Ⓑ. A closer examination of the two "four-level schemes" reveals that in experiment Ⓑ, the low-frequency, and in Ⓐ the high-frequency ENDOR component is more intense (cf. [33]). This behavior is independent of the sign of the HFC constant.

Interestingly, cross-relaxation processes of nuclei with large hyperfine anisotropies, occurring, e.g., in ^{13}C-enriched molecules, can also be detected through nuclei (e.g. protons) in these molecules which do not normally exhibit cross-relaxation effects because of their low anisotropy. This transfer arises because the unpaired electron in organic radicals couples with all magnetic nuclei to give a multispin ensemble. It should be mentioned that investigations of this type—similar to the general TRIPLE effect—allow determination of the relative signs of HFC constants. For more detailed explanations, the reader is referred to the original literature[18b,34].

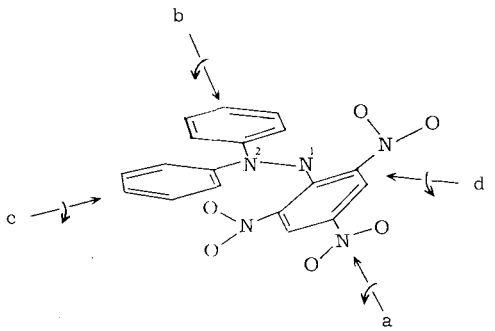
Deuterium (^2H)

In multinuclear ENDOR spectra, deuterons can often be detected with an intensity comparable to that of protons, despite their small magnetic moment (Table 1) (cf. Figures 5 and 9)[19]. Because of the markedly lower hyperfine anisotropy, the optimum ^2H-ENDOR effect occurs at lower temperatures than the ^1H-ENDOR effect. ^2H-ENDOR signals are usually narrower than those of ^1H-ENDOR, which is advantageous for the resolution of, e.g., quadrupole splittings ($I_D = 1$) in liquid crystals (see Section 4).

Nitrogen ($^{14,15}N$)

Since the first successful ^{14}N-ENDOR experiment by *Leniart* et al. in 1970[35], ^{14}N-ENDOR spectroscopy has found growing interest especially in applications to biological systems (cf. also Section 7). The "ENDOR behavior" of a ^{14}N nucleus within a π system is comparable to that of the ^{13}C isotope in a similar environment; the additional quadrupole relaxation of ^{14}N with $I_{^{14}N} = 1$ can, in general, be neglected[7d] since the anisotropic hyperfine interaction provides the main contribution to the relaxation (possible quadrupole effects can be recognized by comparison with ^{15}N-labeled molecules, since this isotope has no quadrupole moment ($I_{^{15}N} = 1/2$)).

Two particularly interesting N-ENDOR investigations will be mentioned here. The first, a study of the "Goldschmidt radical" (*N,N*-diphenyl-*N'*-picrylhydrazyl) by NMR, EPR, ENDOR, and TRIPLE techniques allowed four different dynamic processes to be distinguished on the NMR and ENDOR time scales (denoted by a—d in **1**). The kinetic data were determined by ^1H-ENDOR and ^2H-NMR spectroscopy after ^{15}N-ENDOR and TRIPLE experiments, among others, enabled the complete determination of the HFC constants and their signs[17].



The second, ^{14}N-ENDOR study of the pyrazine radical anion deserves special attention, because here it was shown for the first time that liquid ammonia is well suited for the generation of stable radical anions and for EPR/ENDOR spectroscopy (very good signal-to-noise ratio and efficient TRIPLE and cross-relaxation effects allowing determination of the relative signs of ^{14}N- and ^1H-HFC constants)[34].

Alkali Metal Ions ($M^{\oplus}$)

As is well known, in reactions involving organic ions the influence of the "counterion" on the yield and stereo-

chemistry of the products plays an important role. For this reason, knowledge of type and structure of ion pairs is of considerable interest—also for preparative chemistry. For investigations of *radical* ion pairs, ENDOR spectroscopy has proven especially valuable, because not only the "organic" anionic moiety but also the counterion thus become accessible to direct observation. *Lubitz* et al. were able to detect ^{7}Li-, ^{23}Na-, ^{85,87}Rb-, and ^{133}Cs-ENDOR signals in the metal ketyls of fluorenone[36a] (cf. Fig. 12). The example of the Na ketyl demonstrates how well the heteronuclear TRIPLE resonance effect works[36b]; a proton line is pumped, and the ^{23}Na-ENDOR signals react too! Interestingly, the sign of the sodium HFC constant changes on cooling the solution from ca. 230 K to 170 K. Clearly the structure of the ion pair shows a pronounced dependence on the nature and temperature of the solvent. When contact ion pairs are formed, the spin density changes within the fluorenone ketyl radical and at the metal itself could be correlated with properties of the counterion, and conclusions about the structure of the ion pairs were drawn from INDO calculations.

^{39}K-ENDOR signals can only be detected in chelate complexes with large spin density at potassium because of the very small magnetic moment of ^{39}K (see Table 1). Figure 12 shows the ^{39}K-ENDOR line pair of 1,2-dimesitoylbenzenepotassium[36a]. ^{85}Rb-ENDOR signals were observed for the first time in a similar complex[36c].

Fluorine (^{19}F), Phosphorus (^{31}P), Silicon (^{29}Si), Tin (^{117,119}Sn), Boron (^{10,11}B), Aluminum (^{27}Al), and Thallium (^{203,205}Tl):

Figure 13 represents a small "spectral atlas" of ENDOR signals of nuclei other than protons, not dealt with hitherto. The ^{19}F-ENDOR effect was first mentioned by *Allendoerfer* and *Maki*[37] and discussed later in detail by *Lubitz* et al.[38]. In collaboration with *Haas* et al.[39], we identified the CF_3S-substituted pyrrolyl radical shown in Figure 13 (top left) by ^{14}N- and ^{19}F-ENDOR spectroscopy. ^{31}P-ENDOR spectroscopy was first reported by *Stegmann* et al.[40]. With *Dimroth* et al.[7d,41] we detected ^{31}P-ENDOR signals in a radical generated when 2,4,6-triphenylphosphabenzene was allowed to react with 2,4,6-triphenylphenoxyl (Fig. 13, top right). Whereas the ^{31}P signals can be identified *unambiguously* (line separation $2\nu_{^{31}P}$), the nature of the radical formed is still unknown. In collaboration with *Stegmann* et al.[24,42] we obtained ^{203}Tl- and ^{205}Tl-ENDOR signals for the first time from a complex of an *o*-semiquinone and a diorganothallium(III) compound (Fig. 13, bottom left). In cooperation with *Bock* et al.[16], ^{29}Si-ENDOR signals in organosilicon radicals with natural isotopic abundance were detected for the first time (Fig. 13, bottom right). With *West* we obtained not only ^{29}Si- but also ^{13}C-ENDOR resonances of four- and five-membered cyclosilanes with natural isotopic abundance[43]. The re-

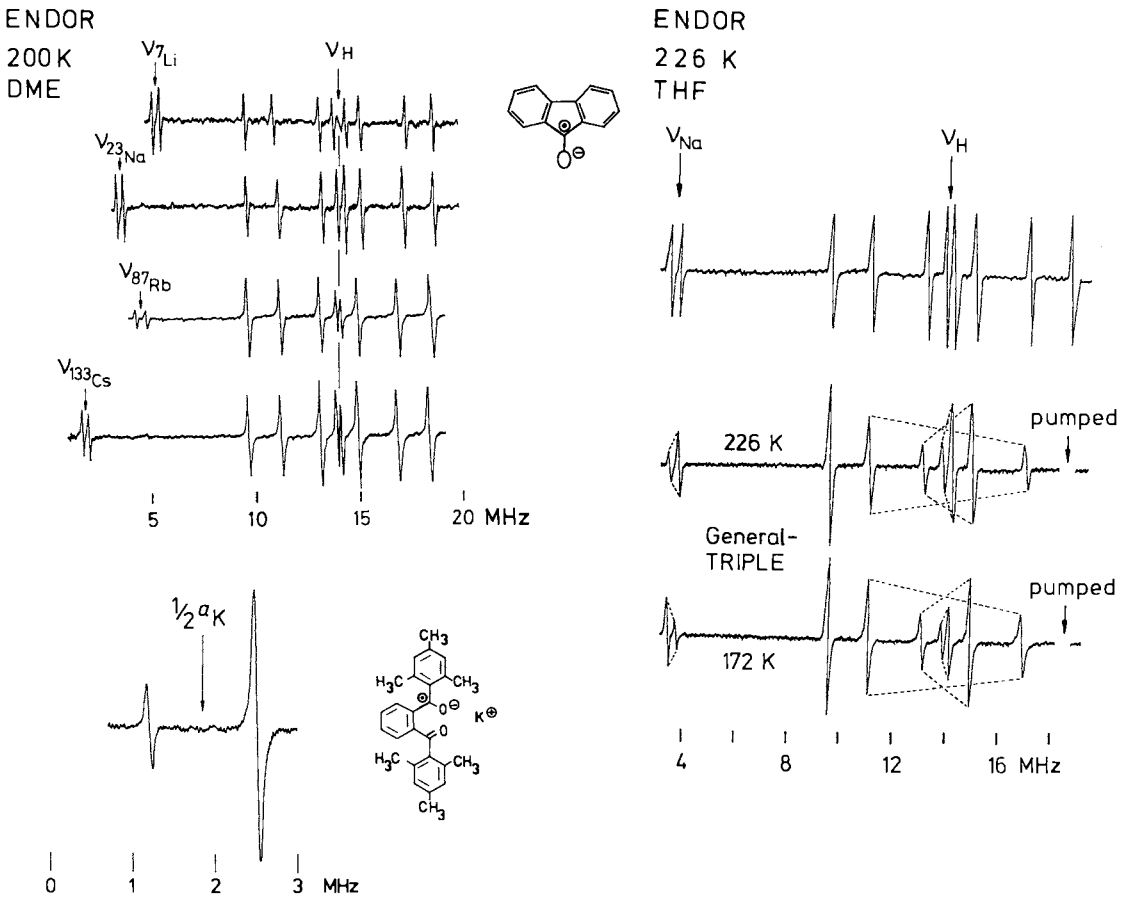


Fig. 12. Alkali metal- and ^{1}H-ENDOR-spectra of fluorenone metal ketyls; for the ^{39}K-ENDOR experiment 1,2-dimesitoylbenzenepotassium was employed. The general TRIPLE spectra of the fluorenone sodium ketyl clearly show that the HFC constant of the ^{23}Na cation changes sign on cooling from 226 K to 172 K (cf. [36a,b]).

sults yielded information about the particularly interesting bonding properties of these systems.

The progress of ENDOR spectroscopy is also revealed in its continuing extension to novel magnetic nuclei. Thus, *Stegmann* et al.[44] recently reported successful ^{117}Sn- and ^{119}Sn-ENDOR experiments on *o*-benzosemiquinones with triphenyltin(IV) counterions. *Kaim* and *Lubitz* observed ^{10}B-, ^{11}B[45a]-, and ^{27}Al[45b]-ENDOR signals for the first time in diazaarene radical anions with the corresponding trialkylmetal species coordinated to the nitrogen atoms.

In a theoretical study of the ENDOR sensitivity of various magnetic nuclei published in 1981[7d], predictions were made about the chances of obtaining ENDOR signals of further, very interesting nuclei such as ^{17}O, ^{33}S, and

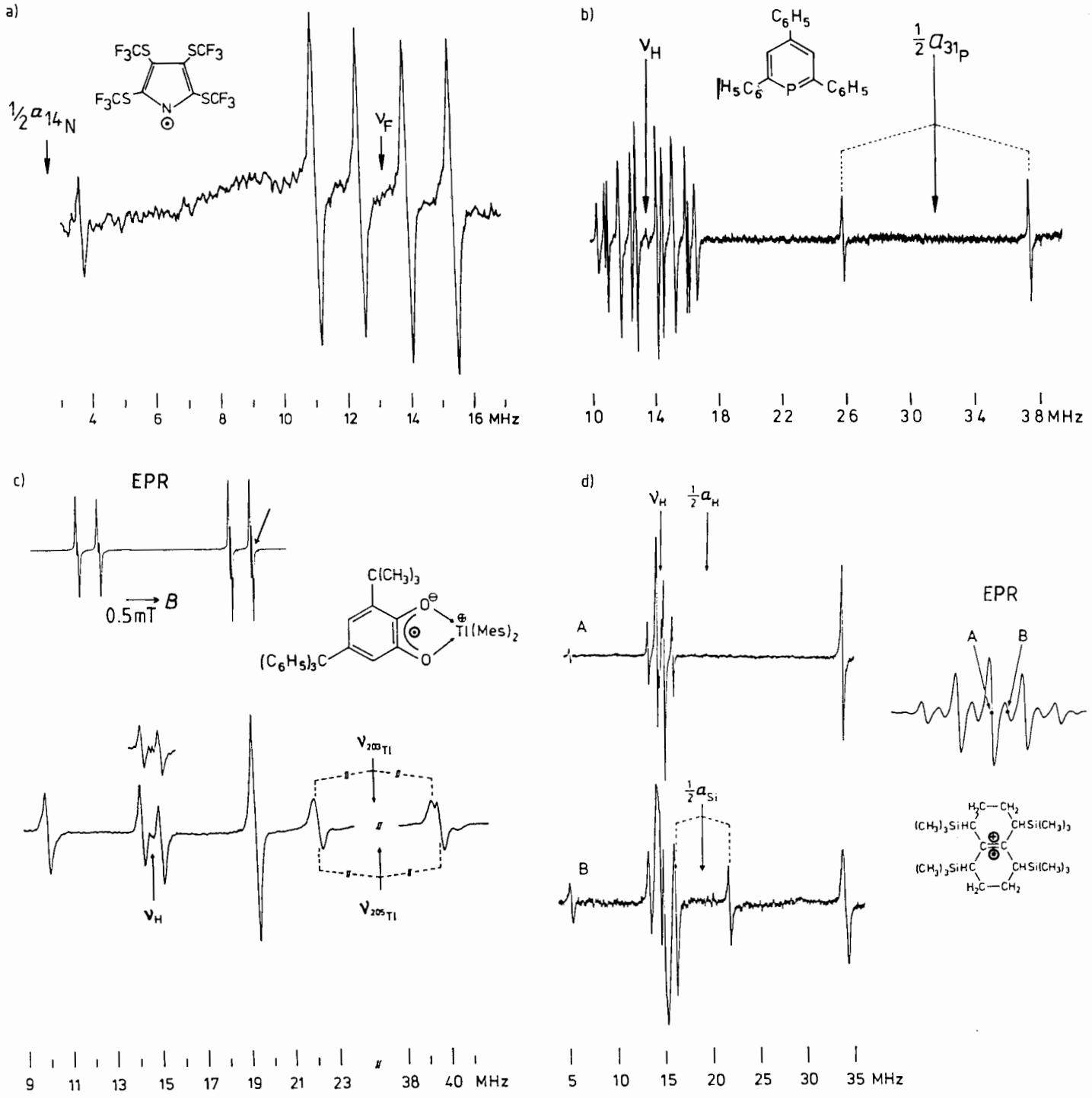


Fig. 13. ENDOR spectra with signals from various nuclei other than protons (see text). Measuring conditions a) ^{19}F: in mineral oil, 330 K; b) ^{31}P: in toluene with 2,4,6-triphenylphenoxyl, 225 K; c) ^{203,205}Tl: in tetrahydrofuran, 260 K; d) ^{29}SI: in dichloromethane, 235 K.

$^{35,37}Cl$ which exhibit usually large quadrupole couplings. It was estimated that ^{17}O- and ^{33}S-ENDOR spectroscopy in solution, which is also biologically relevant, will presumably only be feasible with a few molecules of particularly suitable structure.

4. ENDOR Spectroscopy in Liquid-Crystalline Solutions

The ENDOR experiments in isotropic fluid solution described so far yield—besides the free nuclear frequencies—only *isotropic* HFC constants. To obtain more detailed information about spin density distributions and radical geometries, knowledge of the *anisotropic* hyperfine interactions is often desirable. Although spectroscopy in disordered solids such as powders or glasses can, in principle, afford anisotropic data, the information obtained is rather limited because of the drastic decrease in resolution[46]. On the other hand, all isotropic and anisotropic data are generally accessible from single crystal studies where paramagnetic "guest molecules" are incorporated in sufficient dilution into diamagnetic "host crystals". Nevertheless, apart from the considerable time involved in growing single crystals and their spectroscopic examination, diamagnetically diluted single crystals can be prepared only for a few paramagnetic systems. The use of *liquid crystals* as solvents combines the advantages of spectroscopy in solution (high resolution) and in single crystals (anisotropic interactions are not averaged out). Liquid crystals are suitable as anisotropic solvents because their long-range order is conferred to solute molecules[47]. *Nematic phases* have found extensive applications in NMR[48] and in EPR spectroscopy[15] since they can readily be aligned macroscopically by a magnetic field of about 0.2 T[49]. *Smectic A phases* cannot be aligned directly by a magnetic field, but can in a few cases be aligned indirectly by slow cooling of a precursor nematic phase. "Freezing" the preferential direction then permits investigation of angular dependences[50]. Figure 14 shows schematically the nematic and the smectic A phase of the liquid crystal 4-cyano-4'-octylbiphenyl (8CB). That smectic A phases are well suited for ^1H- and ^2H-ENDOR investigations was shown for the first time using *Coppinger*'s radical[51].

The partial alignment of solute radicals in liquid-crystalline phases, which can be described by an ordering matrix[49], results in a shift Δa of the measured hyperfine coupling constants due to an anisotropic contribution[15]. For the simplest case of axial symmetry about an axis z, the relation is

$$\Delta a = \bar{a}_{nem} - a_{iso} = O_{zz} A'_{zz} \qquad (5)$$

Here O_{zz} is the order parameter, which can have a value between -0.5 and 1 ($O_{zz}=1$ corresponds to complete alignment), and A'_{zz} the axial component of the dipolar hyperfine interaction. Depending on what additional information is available, the experimental data allow conclusions to be made about the degree of ordering, the preferred direction of alignment, or the anisotropic hyperfine interaction. Measurements in liquid crystals can also serve to

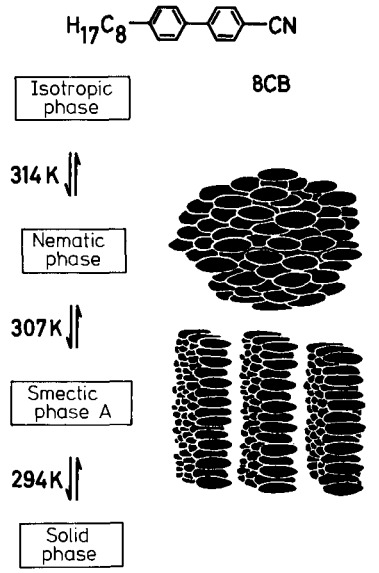


Fig. 14. Schematic representation of different liquid-crystalline phases of 4-cyano-4'-octylbiphenyl (8CB).

lift accidental equivalences of HFC constants, as the ENDOR spectra of the 2-methylphenalenyl radical demonstrate (Fig. 15). In the isotropic phase (top spectrum) the methyl and the small ring-proton HFC constants have coincidently almost the same value. On passing to the smectic A phase (bottom spectrum), however, a marked splitting is observed since the anisotropic shifts act in opposite directions. The splitting which is observable in the region of the large-ring proton HFC constant is due to an additional alignment of the molecules caused by the methyl substituent[52].

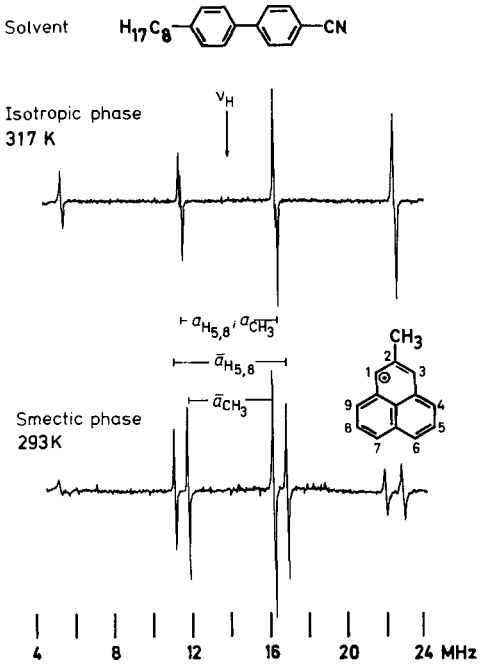


Fig. 15. ENDOR spectra of the 2-methylphenalenyl radical in the liquid crystal 8CB. Whereas the isotropic HFC constants of the methyl protons and the protons in positions 5, 8 are (coincidently) almost equivalent, a marked splitting of the resonance signals appears on passing from the isotropic to the smectic phase (cf. [52]).

In liquid-crystalline solutions the quadrupole interaction of nuclei with spin $I \geq 1$ (^{2}H, ^{14}N) becomes significant. Similarly to NMR spectroscopy, but in contrast to EPR spectroscopy, this interaction gives rise to splittings of ENDOR lines in oriented samples (or in solid solutions). *Dinse, Möbius* et al.[53] detected such quadrupole splittings in ^{14}N-ENDOR lines for the first time in nitroxide radicals in "Licristal Nematic Phase IV". According to the simplified relation (6)

$$\delta_Q \cong \tfrac{3}{2} O_{xx} e^2 q_{xx} Q/h \qquad (6)$$

($I = 1$, neglecting the asymmetry parameter), the quadrupole splittings δ_Q depend on the degree of ordering, the orientation of the bond axes, and the quadrupole coupling constant $e^2 q_{xx} Q/h$[19]. Figure 16 shows ENDOR spectra of the benzil semidione radical anion (unlabeled as well as deuterated in the *para*-positions) in the liquid crystal 8CB[54]. In the ^{2}H-ENDOR spectrum the quadrupole splittings in the smectic phase can be clearly recognized (spectrum center right, $\delta_Q = 160$ kHz). It may be concluded from the magnitude of this splitting that the C–D bond axes are oriented approximately parallel to the director of the liquid crystal, which is only possible if the molecule has a *trans*-configuration. Furthermore, Figure 16 illustrates the strong dependence of the observed hyperfine and quadrupole splittings upon the angle γ between the director of the smectic phase and the magnetic field. Two measurements in a smectic A phase with the sample not rotated ($\bar{a}(0°) = a + \Delta a$) and rotated by 90° ($\bar{a}(90°) = a - \frac{1}{2}\Delta a$) allow the determination of the isotropic HFC constants and the anisotropic shift Δa under the same experimental conditions. On the other hand, the use of nematic phases requires a measurement of the isotropic HFC constants for comparison, either at a higher temperature in the same solvent or in another solvent, which may of course give rise to errors[50].

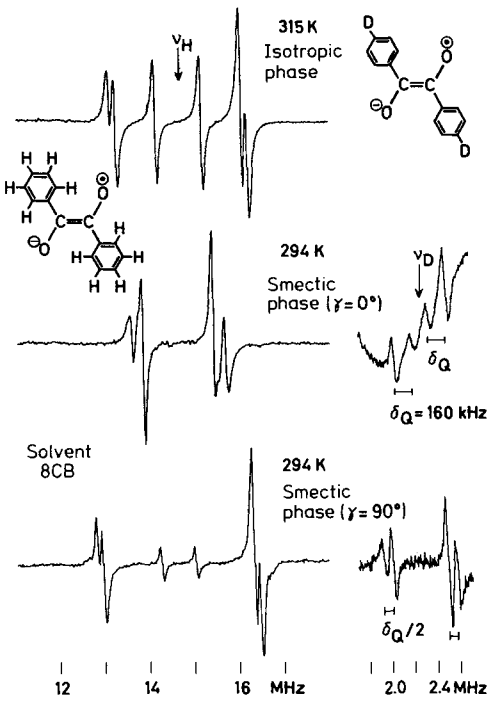


Fig. 16. ENDOR spectra of the benzil semidione radical anion in the liquid crystal 8CB. In the smectic phase, *no* reorientation of the molecules takes place when the sample tube is rotated in the magnetic field—the angular dependence of the resonance positions can be studied, as in single crystals. The selectively deuterated compound shows a pronounced quadrupole splitting (cf. [54]).

Quadrupole splittings of ^{2}H-ENDOR lines were observed for the first time in a deuterated phenalenyl radical[19], and investigations of substituted phenalenyls allowed a determination of the quadrupole coupling constant ($e^2 q_{CD} Q/h = 174 \pm 10$ kHz, asymmetry parameter $\eta = 0.08 \pm 0.04$)[52]. The results available from ^{2}H-ENDOR investigations of radicals and ^{2}H-NMR measurements of diamagnetic molecules[55] show little variation with the ^{2}H-quadrupole coupling constants of C–D bonds. The observed quadrupole *splittings* consequently allow conclusions to be made about radical structures, as has already been discussed for benzil semidione. As another example it should be mentioned that an estimate of the twist angles in the triphenylmethyl radical (ca. 30°) was thus possible[56].

ENDOR investigations of nuclei other than protons (see Section 3) in liquid crystals are subject to severe restrictions because of the high viscosity of nematic, and even more so of smectic, phases. However, ^{13}C-ENDOR signals of high intensity can be obtained in those cases where the ^{13}C-hyperfine anisotropy is exceptionally small, such as in the galvinoxyl and phenoxyl radicals mentioned previously[28] (see Fig. 10). On the other hand, the high viscosity of liquid crystals can sometimes be used to "freeze out" dynamic processes. Thus, in *Coppinger*'s radical a splitting of the ring proton signals, which are normally coalesced in solvents of low viscosity by the rapid rotation of the phenyl groups[51], could be resolved. Another problem is caused by the low solubility of radical ions in liquid crystals. However, it was recently shown[54] that a sufficient concentration of radicals can be achieved in some cases if the alkali metal counterion is complexed by a crown ether or if lipophilic quaternary ammonium counterions are used (cf. also Fig. 16).

5. ENDOR Spectroscopy of Organic Multispin Systems

If a molecule contains more than one unpaired electron, additional magnetic phenomena arise due to *scalar exchange interaction* and *dipolar-electron interaction*. The example of molecules with *two unpaired electrons* will make it clear that the strength of these interactions allows a reasonable classification into "double-doublet radicals", "diradicals", and "real triplet systems". A *diradical* is a species whose spectrum in isotropic fluid solution differs from that of the corresponding monoradical[57]. Thus diradicals are distinguished from *double-doublet radicals*, on the one hand, and real *triplet molecules*, on the other. In the last mentioned, the strong dipolar coupling causes such a large contribution to the electron spin-relaxation that *no* EPR spectrum can be detected in fluid solution[58]. If the exchange interaction is large compared to the hyperfine interaction ($|J| \gg |a|$), rigorous coupling of the unpaired electrons with the spin states $S = 1$, $S = 3/2$, $S = 2$, etc. has to be taken into consideration. The simple "four-level scheme" of a doub-

let radical has to be replaced by the more complicated energy level diagrams shown in Figure 17. The number of EPR hyperfine components increases since the unpaired electrons are formally delocalized over the whole molecule and couple with all magnetic nuclei. Since the total spectral width remains the same, the spectral line density is increased and the resolution decreased relative to that of the corresponding monoradical (cf. Fig. 19). Here the increased resolution achieved by ENDOR spectroscopy is particularly advantageous. The first successful ^{1}H-ENDOR investigation of diradicals (e.g. *p*-phenylenebisgalvinoxyl) in solution appeared in 1975[60]. According to the ENDOR resonance condition [eq. (3)], *three* ENDOR lines are expected for each set of equivalent nuclei in a diradical with $S=1$ ($|J| \gg |a|$) and $M_S = \pm 1, 0$[61]. It was found that the ENDOR lines of such a diradical, consisting of two equivalent monoradical moieties, appear at the *same* positions as those of the monoradical. However, the ENDOR signals display a marked line broadening and different temperature and saturation behavior because of relaxation processes caused by the dipolar electron interaction. The line expected at the free proton frequency, resulting from

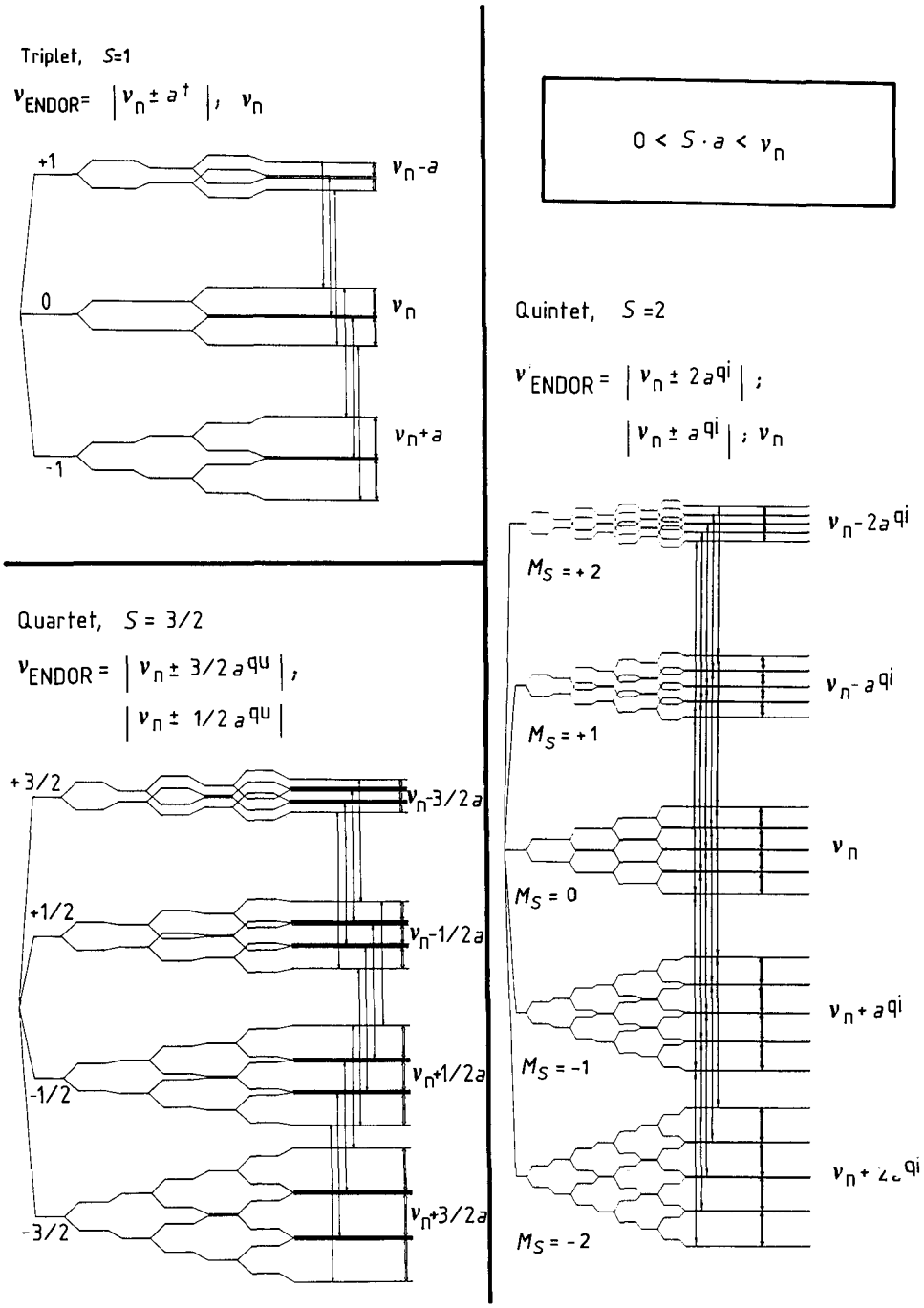


Fig. 17. Energy level diagrams for organic multispin systems in triplet, quartet, and quintet states for the interpretation of the ENDOR spectra reproduced in Figures 18 and 19. Note that the arrows belonging to the EPR transitions $|-1> \leftrightarrow |0>$ and $|0> \leftrightarrow |+1>$ in the diagram of the diradical have the same length (energetically degenerate), see text.

NMR transitions in the $M_S = 0$ manifold, could not be observed. Consequently, the presence of a triplet state cannot easily be established by ENDOR spectroscopic studies in solution, but could be achieved by ^{13}C-labeling[62]. Figure 18 depicts the EPR and ENDOR spectra of the first (doublet) and second (triplet) oxidation steps of the isotopically labeled *p*-phenylenebisgalvinoxyl. As expected (cf. Section 3), only ^1H- and ^2H-ENDOR signals are obtained for the first oxidation step at the lower temperature (210 K), whereas the ^{13}C-ENDOR line pair can only be detected at elevated temperature (250 K) and higher RF power. The pronounced splittings of the signals from the *m*-protons can be accounted for in terms of a sterically induced nonequivalence of these protons. The investigation of the second oxidation step shows *unambiguously* that the spectra have to be assigned to a diradical in the triplet state ($S = 1$) with $|J| \gg |a|$: (a) The EPR spectrum consists of a 1 : 2 : 1 triplet of nonets; hence, each of the two unpaired electrons couples with *all* (eight) *m*-protons and with *both* ^{13}C nuclei. (b) Only mono- and diradicals without a ^{13}C-label or diradicals with two ^{13}C nuclei can absorb in the center of the EPR spectrum. If the external magnetic field is set at the center of the spectrum and ^{13}C-ENDOR signals are observed, then these must arise from doubly ^{13}C-labeled molecules, i.e. diradicals.

Recently, it was shown that ENDOR investigations of unsymmetrical diradicals are also possible[63]. For example, if a nitroxide and a galvinoxyl moiety are linked together, the different *g*-values and HFC constants of the radical moieties have to be taken into consideration. The interpretation of the EPR and ENDOR spectra of such "mixed" diradicals is difficult, especially in the intermediate case $|J| \approx |a|$. A detailed analysis allows the determination of the sign of the exchange integral J[63].

The relaxation processes caused by the dipolar electron interaction give rise not only to line broadening but also to an increase in the electron spin relaxation rate W_e, and thus to a decrease of the ENDOR effect (see Section 2.1). Fluid-solution ENDOR investigations are therefore restricted to diradicals with comparatively small dipolar couplings (zero-field splitting parameter $D \leq 100$ MHz). Measurements in glassy matrices, however, offer an alternative. Here, the dipolar electron interaction is no longer averaged out by Brownian molecular motion but gives rise to a splitting of the EPR transitions $|-1, M_I> \leftrightarrow |0, M_I>$ and $|0, M_I> \leftrightarrow |1, M_I>$[64] which are degenerate in isotropic fluid solution. Incidentally, this degeneracy is responsible for the failure to observe ENDOR lines at the free nuclear frequencies in isotropic fluid solution since both transitions are pumped equally strongly, thus leaving the thermal nuclear spin polarization in the $M_S = 0$ manifold undisturbed (cf. also Fig. 17). In glassy matrices, however, this third ENDOR component can be detected: In general, an intense sharp signal is found at the free proton frequency, and an ENDOR line at the free ^{13}C frequency could even be observed in natural isotopic abundance[65]. Moreover, *one* more, hyperfine shifted ENDOR line, whose position depends on the selection of the pumped EPR component, can be detected for each set of equivalent nuclei. This permits evaluation of the magnitude of the respective hyperfine component together with its sign relative to that of the zero-field splitting parameter[66]. Recently, even investigations of *photoexcited* triplet states (e.g. of naphthalene) were successfully carried out in this way[21].

The example of a triply ^{13}C-labeled trisgalvinoxyl should demonstrate that ^1H- and ^{13}C-ENDOR spectra can also be observed in triradicals[67]. According to the ENDOR resonance condition, *four* ENDOR signals are expected for each set of equivalent nuclei in a quartet state molecule with $S = 3/2$, resulting from NMR transitions in the manifolds $M_S = \pm 1/2$ or $\pm 3/2$ (cf. also Fig. 17). In accordance with theoretical considerations[65], the ENDOR signals belonging to the manifolds $M_S = \pm 1/2$ or $M_S = \pm 3/2$ exhibit different relaxation and saturation behavior. According to the results available so far, threefold symmetry of a quartet state molecule is a prerequisite for a successful ENDOR experiment in fluid solution. If the mutual relations of the individual spin carriers are different (exchange interaction, dipolar coupling), mixed states are formed instead of pure quartet states, which clearly has a crucial influence on the relaxation properties.

Depending on the oxidation state, a molecule with four galvinol moieties can form doublet, triplet, quartet, and quintet states under particular geometrical conditions. A tetraradical with *tetrahedral symmetry* should offer two decisive advantages: The exchange interaction is the same between all pairs of spin carriers, hence the formation of a thermally populated quintet state can be assumed; and the zero-field splitting is equal to zero[68]. These predictions were fully confirmed by the ENDOR investigation of a successively oxidized tetrahedral tetragalvinol, as shown in Figure 19. It can be seen that the resolution of the EPR spectra deteriorates progressively from the doublet to the quintet states (Fig. 19, left), whereas the ENDOR spectra (Fig. 19, right) exhibit all signals expected from the ENDOR resonance condition (eq. (3) with $S = 1/2$ to 2), apart from lines at the free-proton frequency (cf. also Fig. 17).

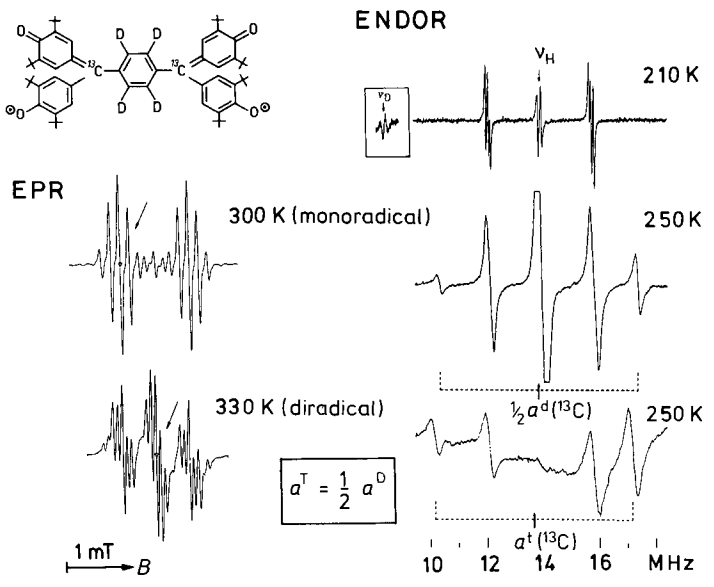


Fig. 18. EPR and ENDOR spectra of the first (monoradical, top and center) and second oxidation step (diradical, bottom) of an isotopically labeled galvinol (cf. [62]). The arrows denote the respective field settings in the ENDOR experiment. The appearance of the ^{13}C-ENDOR signals in the bottom right spectrum establishes the presence of a triplet state (cf. text).

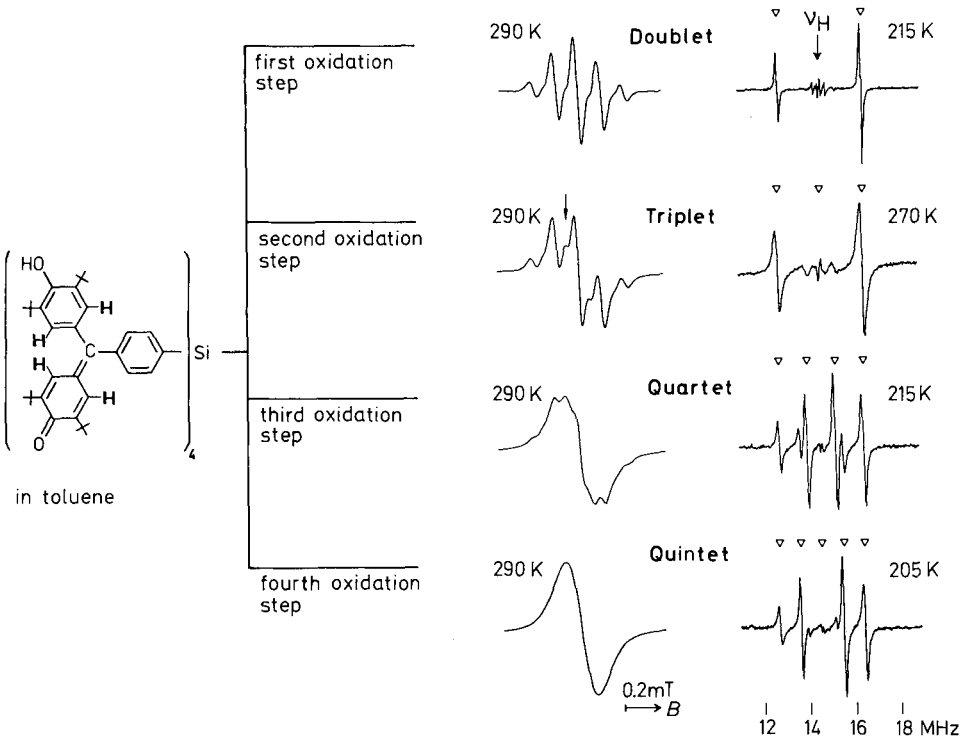


Fig. 19. EPR and ENDOR spectra of the four oxidation steps of a tetragalvinol. Note the deteriorating resolution of the EPR signals with increasing multiplicity, whereas the expected ENDOR signals (marked by triangles) are completely resolved (cf. [68]).

As a matter of fact, only samples from the first and the fourth oxidation steps can be obtained in pure form, whereas the diradical step also contains mono- and triradicals, and the triradical step di- and tetraradicals. The ability of ENDOR spectroscopy to select one species out of a mixture of different paramagnetic molecules can be seen here for the diradical (Fig. 19).

6. Intramolecular Dynamic Processes

ENDOR spectroscopy not only yields information about static molecular properties but may also provide an insight into molecular dynamics, in a similar way to NMR or EPR spectroscopy[7a,69]. Dynamic processes such as hindered rotation of molecular fragments, ring inversions, pyramidal atomic inversions, intramolecular electron transfer, ion-pair interconversions, or torsional oscillations can affect the widths and positions of resonance lines, provided the lifetime of the individual species is of the same order of magnitude as the time scale of the method. The time scale of ENDOR spectroscopy (10^{-9}—10^{-4} s) corresponds to that of EPR, whereas NMR spectroscopy of diamagnetic molecules is a "slower" method (10^{-5}—10^{-1} s). As a typical example, Figure 20 shows the temperature dependence of the high-frequency ENDOR signal of the *ortho*-protons of the 4,4″-dimethyl-*m*-terphenyl radical anion[13]. At high temperatures these protons are spectroscopically equivalent due to rapid rotation of the tolyl groups. With decreasing temperature the signal broadens and splits into two separate signals below the coalescence temperature (157 K), each of which and becomes narrower on further cooling. The rotation of the tolyl groups is now slow compared to the ENDOR time scale, hence the non-

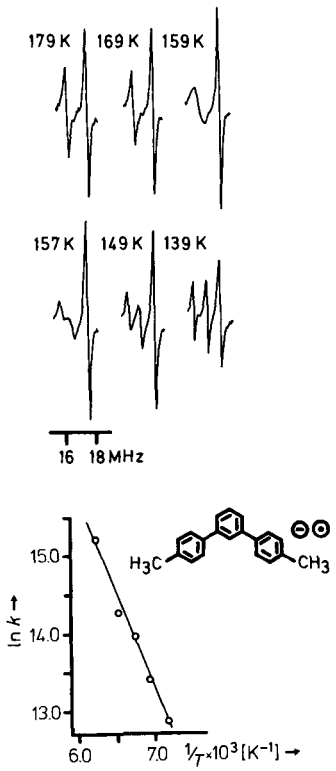


Fig. 20. ENDOR part spectra of the 4,4″-dimethyl-*m*-terphenyl radical anion at different temperatures (coalescence temperature 157 K) in 2-methyltetrahydrofuran. The activation energy and the frequency factor can be taken from the Arrhenius plot (bottom) (cf. [13]).

equivalence of the *ortho*-protons in these groups (twist angle ca. 50°) becomes apparent.

Intramolecular dynamic processes can usually be described as jump processes between two to four distinct species. This implies that the time taken for the jump itself is much less than the mean lifetime of a given species. The determination of rate constants by line-shape analyses is largely analogous to the methods used in dynamic NMR spectroscopy[70]. Line widths or peak separations can be used for the evaluation[71]. The additional line broadening caused by the dynamic effect is (approximately) obtained by comparison with a reference signal of the same sample which does not show this effect. The activation energy E_a of the dynamic process can be determined from the temperature dependence of the rate constant using the Arrhenius equation ($\ln k = -E_a/RT + \ln A_0$; cf. Fig. 20), and the activation enthalpy and entropy are obtained using Eyring's theory (see [72]). In the following, a few applications are mentioned.

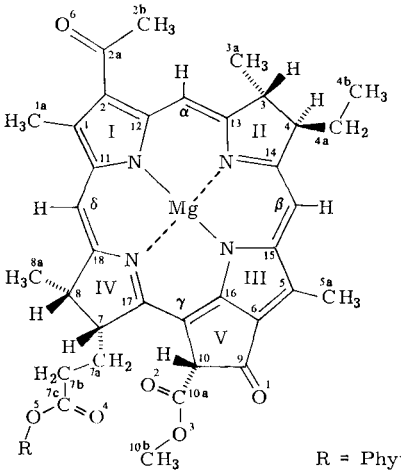
ENDOR spectroscopy was used to investigate the hindered rotation of alkyl side chains in the radical anions of vitamin K_1 and ubisemiquinone[73], as well as of the phenyl groups in silole[72a] and terphenyl radical anions[13,74] and in *N,N*-diphenyl-*N'*-picrylhydrazyl (see Section 3)[17]. In the case of phenylnaphthalene radical anions, a distinction between two types of dynamic processes was possible, namely hindered rotation and ion-pair formation[75]. The hindered rotation of the aroxyl groups in galvinoxyls has been the subject of extensive investigations[28,72b,76], and the mechanism could be largely clarified by systematic variation of the substituents at the central carbon atom and by ^{13}C-labeling experiments (see Section 3). The internal dynamics in tetraaryl- and in bis(biphenylylene)allyl radicals have also been investigated[27,77]. A dynamic process observed in triphenylmethyl derivatives was interpreted as an interconversion of left- and right-handed propeller conformations[78]. The effect of intramolecular cation exchange on ENDOR intensities has been investigated in 2,5-di-*tert*-butyl-*p*-benzosemiquinone ion pairs[79]. A series of papers has dealt with the measurement of temperature dependences of β-proton HFC constants, from which the height of the potential barrier of the hindered rotation was evaluated[80]. As this short survey shows, ENDOR spectroscopy alone or in combination with EPR allows the elucidation of the mechanisms of different kinds of intramolecular dynamic processes as well as the determination of kinetic data and activation parameters or potential barriers.

7. ENDOR Spectroscopy of Biological Systems

Following current developments in many spectroscopic disciplines, ENDOR spectroscopy, too, is increasingly employed to solve biological problems. However, until now ENDOR investigations of biological materials were almost exclusively performed at low temperatures (2—100 K) in powder-like solids; suitable single crystals are rarely accessible[81]. It could nevertheless be shown that interesting structural information can be extracted even from polycrystalline samples by means of ENDOR spectroscopy. This is especially true for protons in freely rotating methyl groups; occasionally ENDOR resonances of protons in other groups and even of nuclei other than protons could also be obtained[82]. Up to now most attention has been paid to paramagnetic derivatives of photosynthetic pigments[83], flavoproteins[84], cobalamins[85], hemo- and myoglobins, and other metalloproteins[81b,82,86].

Undoubtedly ENDOR studies of biological materials would be highly interesting under physiological conditions, i.e. at ambient temperature in aqueous media. According to theory[7d], however, ENDOR investigations of transition metal complexes such as iron-, cobalt-, or copper-containing proteins and coenzymes in solution are *not possible* because of the very unfavorable relaxation properties of these systems. The ENDOR study of metal-free proteins also becomes difficult if the effective molecular volumes are large—because the rotation in solution is no longer fast enough to average out *g*- and hyperfine-anisotropies. For example, a rotational correlation time of 30 ns can be estimated for molecular weights of ca. 100000[87]. As a consequence, only dipolar hyperfine components smaller than 5 MHz are averaged out. Broad and hardly detectable signals similar to powder-type ENDOR spectra are therefore obtained for nuclei with larger anisotropy, even in solution.

Chlorophylls and bacteriochlorophylls play a central role as photopigments in all photosynthetic organisms. As is well known, the photosynthesis consists of a light-induced charge separation, giving rise to the formation of radical cations of primary donors and radical anions of acceptor molecules. ENDOR spectroscopy appears to be a promising method for the identification and structural characterization of these paramagnetic species occurring in the "reaction centers"[88].



Since (bacterio-)chlorophylls and pheophytins participate in the primary step, an investigation of the pigments appeared first to be necessary. As an example, the ^1H-ENDOR spectrum of the radical cation of bacteriochlorophyll a is reproduced in Figure 21 (bottom), from which eleven ^1H-HFC constants can be extracted. The corresponding ^{14}N-ENDOR spectrum yielded all four ^{14}N-HFC constants. Recently ENDOR/TRIPLE studies of the in situ light-induced radical cation of the primary donor $P^{\oplus\odot}$ in the "reaction centers" of several photosynthetic

bacteria were performed in aqueous solution at 25 °C[89,90]. In Figure 21 (top) such an ENDOR spectrum of $P_{870}^{\oplus\ominus}$ (*Rp. sphaeroides* R-26) is depicted. From this "genuine" solution spectrum, seven isotropic ^{1}H-HFC constants could be extracted and were assigned to certain positions in bacteriochlorophyll a by comparison with data from selectively deuterated reaction centers from biosynthetically labeled bacteria. This investigation made a contribution to the contested question of the formation of a "supermolecule"[90] ("special pair" hypothesis[83]).

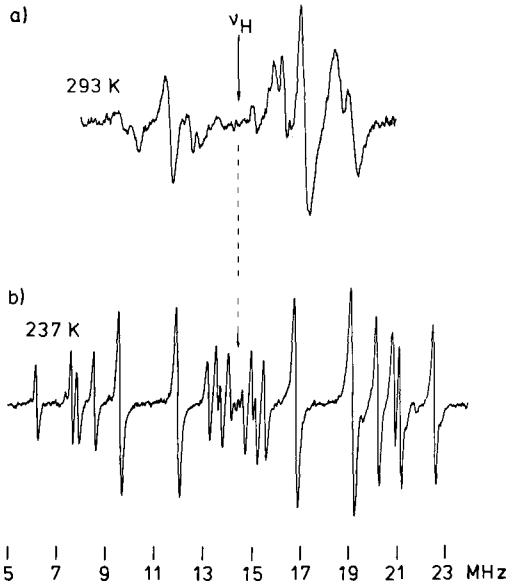


Fig. 21. a) ^{1}H-ENDOR-in-solution spectrum of "reaction centers" from the bacterium *Rp. sphaeroides* R-26 irradiated in situ in the ENDOR cavity; the radical cation $P_{870}^{\oplus\ominus}$ is observed (TRIS buffer, pH = 7.5, lauryl (dimethylamine oxide)). b) ^{1}H-ENDOR spectrum of the radical cation of bacteriochlorophyll a isolated from *Rp. sphaeroides* R-26; generation of the radical cation BCHl $a_p^{\oplus\ominus}$ in CH_2Cl_2/CH_3OH by oxidation with iodine (cf. [89,90]).

Das et al.[73] reported ENDOR-in-solution investigations of the paramagnetic forms of several biologically important quinones such as ubiquinone and vitamins K_3, K_1, E. Four ^{1}H-HFC constants could be determined in electrolytically generated ubisemiquinone-10[91]. Since ubiquinone acts as an electron carrier in many life processes, a comparison with in situ ENDOR spectra of the radical in biological material would be appropriate. However, the solid-solution ENDOR spectrum of ubisemiquinone obtained by *Okamura* et al.[92] from iron-free reaction centers of the bacterium *Rp. sphaeroides* R-26 has not yet been completely analyzed. We were able to determine spin density distributions in radical cations of model compounds of the vitamin E series and observed interesting dynamic effects in ENDOR studies in collaboration with *Sutcliffe* et al.[93].

In the spirit of the introductory remarks to this section, the authors' group has engaged in ENDOR investigations of flavins and flavoenzymes for about two years. These enzymes, as redox catalysts, function as mediators between one- and two-electron transfer steps (more accurately, two one-electron transfer steps) in biological electron-flow processes, e.g. between the NAD/NADH and the ubiquinone system[94]. In fact, the one-electron steps give rise to flavin radicals which can be studied by EPR and ENDOR spectroscopy.

Recently, high-resolution ENDOR/TRIPLE spectra of several model compounds, namely the radical cations of isoalloxazine derivatives, were obtained in solution for the first time. Complete sets of the ^{1}H- and ^{14}N-HFC constants, including their signs, could be determined and assignments made by selective deuteration[95]. Figure 22 shows the ^{1}H-, ^{2}H-, and ^{14}N-ENDOR spectra of the radical cations of several lumiflavins.

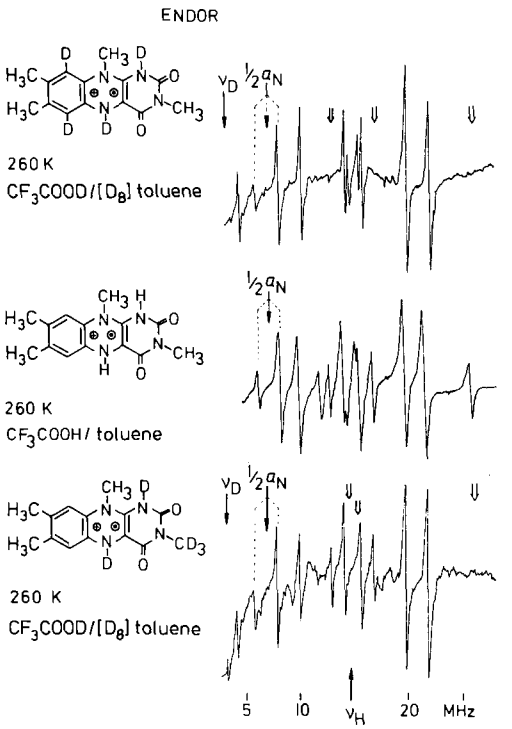


Fig. 22. ENDOR spectra of lumiflavin radical cations. Besides signals from ^{1}H and ^{14}N, ^{2}H-ENDOR signals of selectively deuterated molecules appear in the spectra. The arrows indicate the resonance positions of ^{1}H-ENDOR lines that disappeared upon deuteration (cf. [95]).

Although lumiflavin is considered to be a suitable model system in flavin biochemistry, it is always a challenge to apply the spectroscopic techniques to genuine native, biological material. Since roughly the end of the nineteen-sixties, interesting ENDOR investigations of flavoenzymes in solid matrices have been published, especially by *Hyde* and *Ehrenberg*[84]; these allowed, in part, definite conclusions to be drawn about the nature of the bond between the prosthetic groups and apoproteins. Recently we have been able to perform detailed ENDOR experiments in solid matrices, making use of a substantially improved spectrometer[96]. *Warburg*'s "old yellow enzyme", a NADPH dehydrogenase that can be isolated from brewer's yeast, was investigated[96]. In collaboration with *Kroneck* et al.[96] we studied a methanol oxidase from *Candida boidinii* and an enzyme/pseudosubstrate interaction. Finally, with *Müller*[96] we investigated several flavodoxins (from *Azotobacter vinelandii* and *Megasphaera elsdenii*). For example, Figure 23 shows the EPR, ENDOR, and special TRIPLE spectra of NADPH dehydrogenase, whose radical was generated by irradiation in the presence of ethylenediami-

netetraacetic acid (EDTA) as electron donor. In accord with previous investigations[84a] the radical species could be identified as the radical anion of "flavin mononucleotide" (FMN) by comparison with the authentic model compound. Investigations of the line width as well as the dependence of the line shape of the solid-solution ENDOR spectra of flavoenzymes on the external field setting yielded information about the geometry of the isoalloxazine ring system and about the intramolecular mobility of the prosthetic group in the "pocket" of the apoprotein. However, ENDOR investigations of flavoenzyme radicals in fluid aqueous solution have not yet been successful.

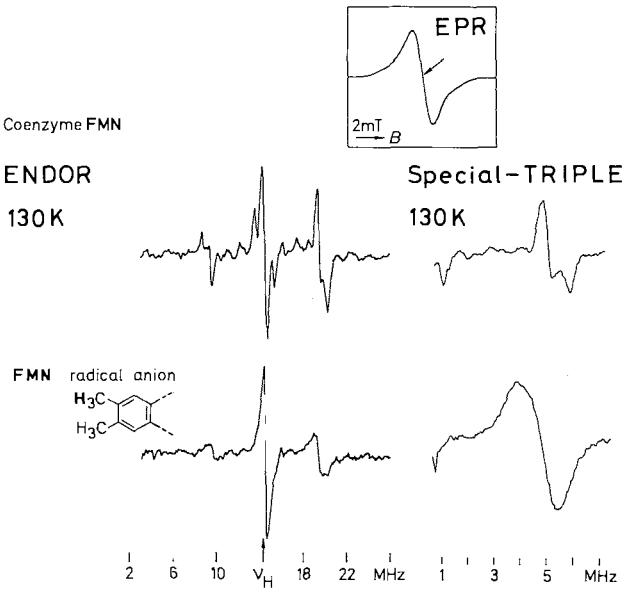


Fig. 23. ENDOR and special TRIPLE spectra of the radical in "old yellow enzyme" (NADPH dehydrogenase from brewer's yeast) generated by irradiation in the presence of an electron donor (20 mM TRIS buffer, pH 9.0, 10 mM EDTA, 80 min irradiation). A comparison with the spectra of the FMN radical anion (below) allows identification of the degree of protonation in the prosthetic group (cf. [96]).

8. Limitations and Outlook

This review indicates that the double resonance method ENDOR with its extensions to TRIPLE is, for many applications, far superior to conventional EPR spectroscopy. In particular, the following points should be emphasized: its high resolving power, its potential as an elegant method of determining the relative signs of coupling constants, its ability to identify different kinds of nuclei and to study their properties individually, the possibility of selecting different species in fluid solution or differently oriented molecules in solid matrices, and finally its ability to determine the spin state, i.e. the multiplicity of organic polyradicals. It has to be borne in mind, however, that applications of the ENDOR technique have so far been limited. Because of their unfavorable relaxation properties, organic radicals with large g-value anisotropies, and/or nuclei with large hyperfine anisotropies or quadrupole couplings, as well as polyradicals with large dipolar electron interactions give rise to scarcely detectable ENDOR effects in solution.

Although the list of references in this article is by no means exhaustive, it is clear that to date less than a dozen research groups have been intensively engaged in ENDOR-in-solution spectroscopy. Not even the development of commercial computer-controlled instruments could change the fact that ENDOR spectroscopy is not a routine method. Successful work still requires long-standing experience; the more so if samples more complicated than "standard" (phenalenyl, galvinoxyl) requiring careful optimization of sample preparation and of spectrometer settings are to be studied. Nevertheless, the ENDOR technique will be used more frequently since it is an indispensable aid to solving difficult structural analysis problems in paramagnetic molecules.

As far as the further development of conventional (continuous wave) ENDOR spectrometers is concerned, an improvement of the ENDOR cavity using the NMR coil—the centerpiece of the spectrometer—appears to be particularly desirable in our opinion.

Whereas pulsed NMR spectrometers have found widespread use, only very recently have pulsed EPR spectrometers become commercially available[97]. It should be mentioned that spin-echo ENDOR experiments on single crystals have already been performed successfully[98]. In this double resonance technique, an RF pulse is applied at a particular time in the electron spin-echo pulse sequence, and a plot of echo intensity versus radio frequency then yields the ENDOR spectrum[99]. The spin-echo technique might extend the range of applicability of the ENDOR method substantially, since its dependence on a critical balance of the RF and microwave powers and the various relaxation rates has been overcome[98]. It should also be possible to perform spin-echo ENDOR experiments in solution, but the short relaxation times and the high powers thus required give rise to experimental difficulties. Finally, it should be noted that the use of flow systems should also allow ENDOR investigations of short-lived radicals. In this context, an increase in sensitivity using spin polarization techniques ("CIDEP-enhanced ENDOR") in the photolytic in situ generation of radicals might be helpful[22b, 100]. However, these novel techniques still demand extensive development efforts and require a more sophisticated experimental set-up. The chances that these highly interesting variants will become routine methods in chemical laboratories in the foreseeable future are therefore even lower than that of conventional ENDOR spectroscopy.

H. K. is grateful to his friends and colleagues from the realms of physics for awakening his—however, not always untroubled (!)—love of ENDOR spectroscopy and for keeping it alive through their readiness to help. In particular, Dr. R. Biehl, Dr. K. P. Dinse, Prof. Dr. K. Möbius, Dr. M. Plato, as well as Dr. F. Lendzian and Dr. C. Winscom should be mentioned. Acknowledgement is also made to the members of our group mentioned in the respective references and to Mrs. E. Brinkhaus and Mrs. J. Krüger for their collaboration. B. K. gratefully acknowledges a Liebig Stipendium from the Fonds der Chemischen Industrie. H. K. thanks the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie for financial support. W. L. thanks the Deutsche Forschungsgemeinschaft for many years of finan-

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[1] E. Zavoisky, *J. Phys. (Moscow) 9* (1945) 245. Unfortunately, as in nuclear resonance, different acronyms are used synonymously for electron spin resonance (EPR: *E*lectron *P*aramagnetic *R*esonance, and ESR: *E*lectron *S*pin *R*esonance). Here we prefer the designation EPR which is finding increasing usage since it includes – in contrast to ESR – both the contribution from the orbital magnetism and from the spin magnetism.

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[8] The term "rate" (induced rate, relaxation rate) denotes the number of spin flips per unit time, by analogy to "radioactive decay rate".

[9] The relaxation rates W_e and W_n are, in general, determined by the spin-rotational interaction and the modulation of the dipolar hyperfine interaction, respectively: $W_e^{SR}=B/\tau_R$ and $W_n^{END}=A\cdot\tau_R$. The constant $B\propto\sum_i(g_{ii}-g_e)^2$ depends on the g-value anisotropy, whereas $A\propto Tr A'^2$ contains the magnitude of the hyperfine anisotropy.

[10] The saturation conditions are as follows: $\sigma_e=\gamma_e^2 T_{1e}T_{2e}B_e^2\geqq 1$ and $\sigma_n=\gamma_n^2 T_{1n}T_{2n}B_n^2\geqq 1$, where σ_e, σ_n are the saturation parameters, γ_e, γ_n the magnetogyric ratios, T_{1e}, T_{1n} the longitudinal and T_{2e}, T_{2n} the transversal relaxation times, and B_e, B_n the (effective) field strengths; the subscripts e and n refer to the electron and the nucleus, respectively. Cf. J. H. Freed in L. T. Muus, P. W. Atkins: *Electron Spin Relaxation in Liquids*, Plenum, New York 1972.

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Biochemical Aspects of Cholinergic Excitation

By Alfred Maelicke*

In memory of David Nachmansohn (1899—1983)

A prerequisite for every biological system to develop and to continue to function ("to live") is an effective communication between its components, i.e. its cells. This intercellular communication is essentially of a chemical nature: It employs neurotransmitters and hormones as messengers, and receptors as the receivers of transmitted signals. As is typical for all communication systems, biological signal processes usually also utilize only relatively small amounts of material. This general rule, however, does not apply to some synaptic communication systems. One typical exception, for instance, is the nerve-muscle synapse and, in particular, its special form, the nerve-electroplaque synapse of electric fish. These systems, therefore, lend themselves to biochemical studies permitting investigation of the molecular basis of biological communication processes. Thus, the acetylcholine receptor of the plasma membrane of the postsynaptic cell was established as a structurally and functionally rather complicated "transducer system" responsible for both the reception of the chemical message and its conversion into an electrical activity of the receiving cell.

1. Introduction[11]

The central event in the process of chemical excitation is the conversion of the chemical signal into the primary response of the cell. In the case of cholinergic excitation of peripheral muscle cells, a single molecule, namely the nicotinic acetylcholine receptor is responsible for both signal reception and primary response (Fig. 1): through binding of the neurotransmitter acetylcholine released from the associated nerve ending, the receptor receives the chemical message. Short-lived openings of the receptor-integral ion channel constitute the initial reaction to this stimulation, the primary response. This integration of the receiving and the responsive unit into a single protein structure seems to be typical for many ligand-activated ion channel proteins of excitable cells. The acetylcholine receptor, as the biochemically best characterized of all neuroreceptors, may therefore serve as a model system for other ligand-activated ion channels such as those of the central nervous system.

Although the basic reactions in the course of cholinergic excitation and the molecular components participating in these are rather well known (Fig. 1), a molecular mechanism for cholinergic excitation has not yet been established. In particular, it is not yet understood which structural properties enable the receptor to differentiate between agonists (channel activating ligands like acetylcholine) and antagonists (ligands without channel activating properties) and how the binding of the transmitter (or its agonists) is linked on the molecular level to the opening and closing of the receptor-integral ion channel.

In the following these questions will be discussed on the basis of the available biochemical data on the interaction of the receptor with its ligands. Since the acetylcholine receptor is a component of biological systems, such a discussion must also include its physiological role. We shall therefore systematically deal with the physiological, structural, and biochemical aspects of such an interaction. The model finally developed for the mechanism of cholinergic excitation is in good agreement with the existing data.

This article is in no way intended to be comprehensive. When neighboring areas are touched upon the reader is referred to the quoted review articles. Additional information on the biochemical aspects can also be found in several recent reviews[1-10].

2. Electrophysiological Basis

The primary physiological response of the postsynaptic cell to the stimulus exerted by acetylcholine is a brief change in its membrane potential in the region of the synapse. This is caused by openings of a specific ion channel which is an integral part of the receptor protein[12-14]. The channel has an effective pore size of approximately 7 Å and allows all cations with this or smaller ionic radius in the hydrated state to pass through. Thus, under physiological conditions there is a net influx of ions, mainly $Na^{\oplus}$, $K^{\oplus}$ and some $Ca^{2\oplus}$ ions, into the cell during cholinergic excitation.

Macroscopically two types of postsynaptic membrane currents are caused by the presynaptic release of acetylcholine[17-19]: The spontaneous miniature end-plate currents (mepc) are small, have a constant amplitude, and therefore probably result from the release of one "quantum" (often assumed to be the content of one presynaptic vesicle, about 4000—10000 molecules) of acetylcholine. The end-plate currents of usual size (epc) as they are observed after electrical stimulation of the presynaptic nerve ending and the resulting release of acetylcholine, are of larger amplitude and therefore relate to several hundred quanta of transmitter. The half-lives of end-plate currents caused by cholinergic excitation are of the order of millise-

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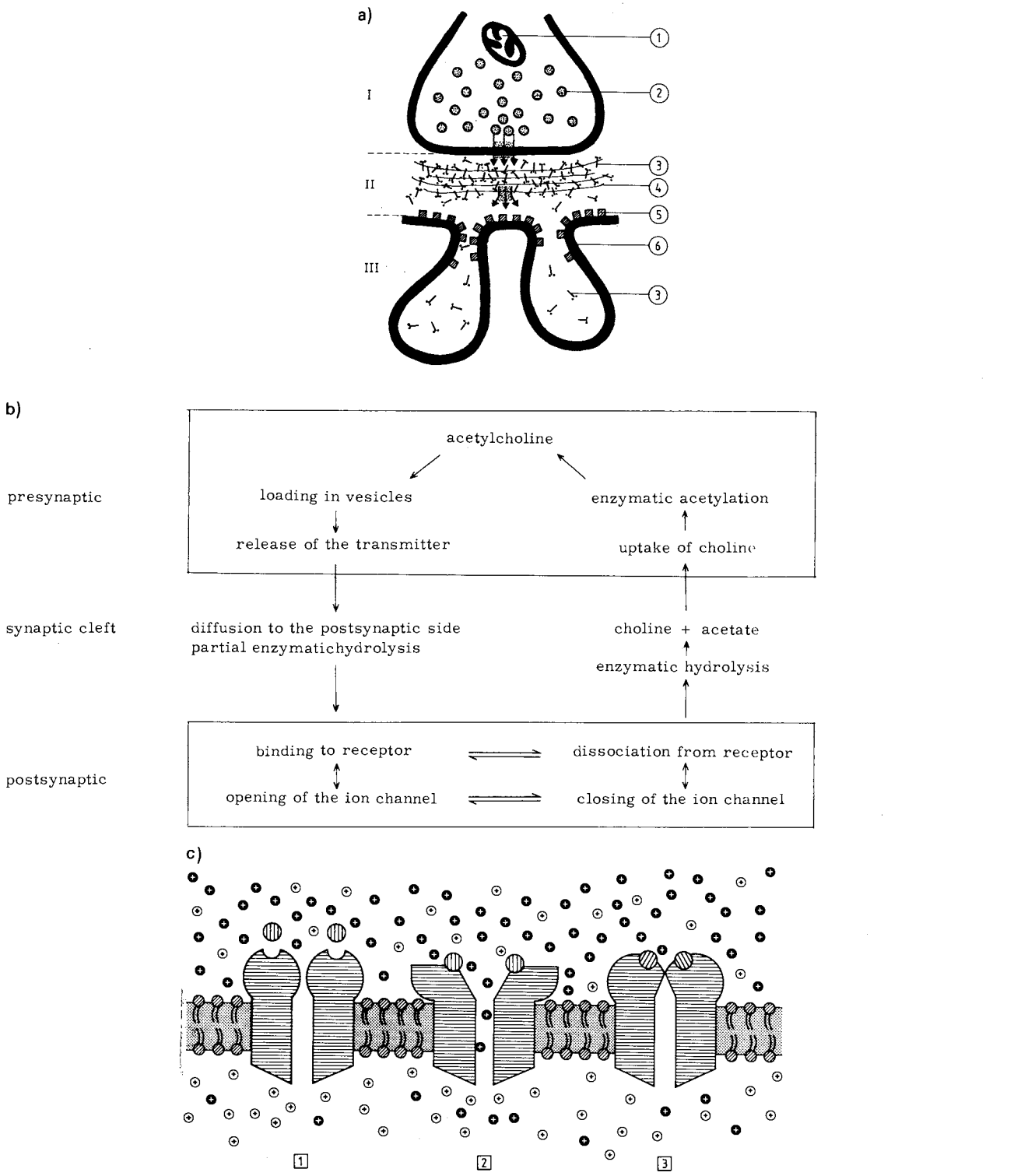


Fig. 1. a) Schematic presentation of a cholinergic synapse. Typical structures of the presynaptic nerve endings I are, apart from the mitochondrion ①, the transmitter-filled vesicles ②. The postsynaptic areas III of mammalian muscle cells are characterized by deep folds: The acetylcholine receptors ⑤ are mostly found in the button-like protrusions of the muscle cell plasma membrane ⑥. Acetylcholine esterase ③ is found in its different forms both in the synaptic cleft and also in the folds of the postsynaptic membrane. The collagen-like tail of some of its forms provides the esterase with additional affinity for the basal lamina ④. It is believed that the contents of one presynaptic vesicle (about 4000–10000 molecules of transmitter) is responsible for the smallest response observed (miniature end plate potential). The synaptic concentrations of acetylcholine receptor and esterase are of the same order of magnitude.—b) Sequence of reactions in the course of an event of cholinergic excitation. An axonal impulse initiates the presynaptic release of transmitter. Following diffusion through the narrow synaptic cleft, acetylcholine binds to its specific receptor, thereby causing short-lived openings and closings of the receptor-integral ion channel. Free and dissociated acetylcholine is hydrolyzed to choline and acetate by the acetylcholine esterase present in the synaptic cleft. Choline is taken up into the nerve ending by the presynaptic choline uptake system, is converted back into acetylcholine by cholineacetyltransferase (with acetyl-CoA and ATP), and reloaded into synaptic vesicles.—c) Model depicting three "states" of the receptor-regulated cation channel. In the absence of transmitter ◍ (or its agonists) the cation channel exists in the closed (*"resting"*) state (State [1]). Through binding of two transmitter molecules the ion channel is briefly opened (*"activated"*), thereby permitting the flow of certain cations along the existing ion gradients (State [2]). Under physiological conditions, predominantly $Na^{\oplus}$ ions flow into the cell thereby causing a depolarization of the plasma membrane. If transmitter remains bound to the receptor over longer periods of time (caused by high concentrations of transmitter as a result of increased transmitter release or of inactivated esterase), the ion channel converts to a persistently closed (*"desensitized"*) state (State [3]).

conds and depend on both the temperature and the existing membrane potential[20–26]. The variations in the synaptic cleft of the transmitter concentration during an event of cholinergic excitation have never been measured directly. On the basis of the existing electrophysiological and biochemical data, however, it appears likely that the observed currents are directly linked to the increase and decrease of transmitter concentration in the synaptic cleft. It can be estimated that after its presynaptic release the concentration of transmitter in the cleft briefly increases from the basal concentration of about 10^{-8} M to 10^{-3} M, and then drops back within a few milliseconds to its original level due to enzymatic hydrolysis and diffusion[10,27–31].

By reducing the area of observation and at the same time increasing the sensitivity of the measurements, it has become possible to directly measure the opening and closing of *single* ion channels in the postsynaptic membrane[32,33] (patch-clamp method Fig. 2). Single channel and noise measurements[34–36] have defined the following properties of the receptor-integral ion channel: The electrical conductivity of the open channel is of the order of 25 pS[37]; each channel contributes about 0.3 μV to the depolarization of the postsynaptic membrane. The opening rates of the channel decrease with increasing transmitter concentration to a few microseconds at saturating concentrations of agonist[38,39]. The closing kinetics of the channel are independent of the transmitter concentration; the mean open times of single channels are therefore constant and, depending on temperature and the nature of the ligand (agonist), are in the range of 0.5—5 msec[12,13,24,32,38,40–43].

The observed jumps in membrane conductivity (Fig. 2b) were originally identified as single channel events[32], for despite the same amplitude they differed from event to event in their duration (open time), showing a Gaussian distribution. Recent results[44–49] indicate, however, that the receptor-integral ion channel can exist not only in two states (one closed and one open) but that there exist several states of both the open and closed channel. These states differ in conductivity and mean open time (states of the open channel) or in their inactivity periods (states of the closed channel). At present, there does not exist structural or biochemical correlates to the distinct states of the receptor-channel defined by physiological measurements.

A further basic property of postsynaptic membranes is their ability to desensitize. Desensitization is defined as a decrease in response, i.e. current amplitude, under conditions of constant stimulation[50–56]. This effect can be viewed as a protective measure of the cell against prolonged depolarization. On the basis of their time constants, a fast (in the region of seconds) and a slow (in the region of seconds to minutes) desensitization can be distinguished. Desensitization is a property of the receptor saturated with transmitter or agonist and is reversed after removal of the inducing ligand. The rate of desensitization increases proportionally with increasing concentration of agonist; the effect is accelerated at increased temperatures[57], low $Na^{\oplus}$, or high $Ca^{2\oplus}$ concentration[58], in the presence of certain non-competitive ligands[57,59,60], and by hyperpolarization of the membrane[57]. Since resensitization can occur either quickly or relatively slowly[56,61] it appears that at least two reaction steps must exist, both for desensitization and resensitization[56]. Single channel experiments show that desensitization is not merely due to a decrease in the number of activated channels at the given agonist concentration, but that the properties of the remaining channels are also altered. The desensitized state is characterized by larger mean open times of the remaining channels, groups of opening and closing events, and long periods of inactivity between them[12,61].

This rather elaborate picture of the electrophysiological properties of postsynaptic membranes indicates that the molecule responsible for these properties must be a rather variable and therefore highly developed signal transducing system. Therefore, profound structural, chemical and biochemical studies are required to fully expose the molecular basis of the different functional states of the receptor. At the present level of molecular analysis, only rough structural correlates are available.

3. Pharmacological Basis

The receptor hypothesis developed by *Langley* et al.[62–64] states that substances which do not penetrate into cells

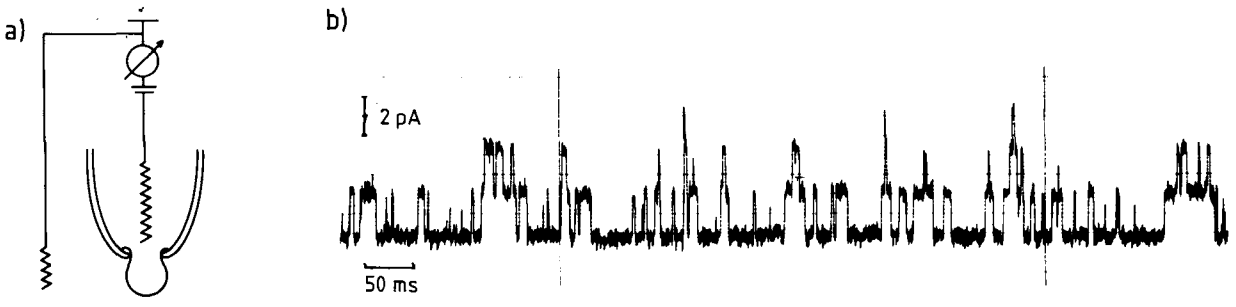


Fig. 2. Acetylcholine-induced changes in the electrical conductivity of single acetylcholine receptor-ion channels. a) According to *Hamill* et al. [33], a small patch of membrane of an embryonic rat muscle cell was sucked into the tip of a measuring pipette in such a way that a seal resistance of several GΩ resulted. The electrical activity of the membrane patch was then recorded under conditions of the voltage-clamp. This method is called "patch clamp" and permits the recording of single channel events from these membranes. The pipette solutions were made as follows: Inner solution 150 mM KCl, 1 mM EGTA, 4 mM HEPES, pH 7.2; outer solution, 150 mM NaCl, 2 mM $CaCl_2$, 2 mM $MgCl_2$, 4 mM KCl, 4 mM HEPES, pH 7.2. The membrane potential was set to −70 mV corresponding to a slight hyperpolarization of the muscle membrane. Temperature 25°C.—b) The measured events were observed after addition of acetylcholine (2 μM) to the outer solution. As can be seen from the different levels of amplitude, double and triple channel events were observed in addition to single channel events (simultaneous activation of two or three receptor channels). These measurements were carried out by Dr. *C. Methfessel*, Universität Bochum.

can influence their function by binding to specific molecular structures on their surface—the receptors. This binding induces physical changes in the receptor (e.g. changes in the conformation or in the charge distribution), which can regulate the properties of the cell membrane or of intracellular reactions.

While pharmacologists view the receptor as a purely operative entity, biochemists link it to the concept of the molecule or molecular complex. This has led to expansions of the pharmacological definition in that for several receptor systems a strong structural link has been established between the actual binding site(s) and the regulatory function affected by these. In the specific system discussed here, the acetylcholine receptor is not only defined as the site or subunit to which the cholinergic ligands bind, but as the whole molecule. This comprises five subunits ($\alpha_2\beta\gamma\delta$) and contains also the cation channel regulated by the ligand binding sites[10-13,31]. As we shall see, this molecular concept of the receptor is advantageous also because there exist several types of ligands of the acetylcholine receptor and these may bind to several structurally distinct binding sites. In contrast, the classical definition of the receptor as a specific binding site could easily lead to confusion if all the different classes of ligands (including modulators) and their binding sites were considered.

According to the classical occupation model[65] there are only two types of ligands which can bind to the same receptor (the same binding site): Agonists whose binding induces a response, and antagonists whose binding does not induce a response but blocks the binding and, thus, the response induced by agonists. On the basis of our present understanding of how receptors function, however, this classification is no longer adequate. Nowadays the following classes of ligands are considered[10,35,36,66-68]:

1) *Agonists*. These, like acetylcholine, briefly increase the conductivity of the end plates for certain cations, thereby reducing the existing membrane potential (they act as depolarizing agents).
2) *Antagonists*. These compete with agonists for binding to the receptor but are not capable of causing an increase in membrane conductivity. Thus, they block in an apparently competitive manner the depolarization induced by agonists.
3) *Partial Agonists*. These possess both antagonist and agonist properties. They cannot produce the maximal increase in conductivity caused by pure agonists.

4a) *Non-competitive Blockers*. These influence the properties of the receptor-regulated ion channel by binding to sites separate from those for pure agonists or antagonists. Typical members of this class of ligands are certain local anaesthetics.

4b) *Direct Channel Blockers*. These block the receptor-regulated ion channel directly, i.e. by binding to site(s) at the channel and separate from those for agonists and antagonists. There does not exist a clear-cut biochemical distinction between direct channel blockers and the previously mentioned non-competitive blockers.

The following models have been developed on the basis of the physiological data to describe the concentration and time dependence of the effects caused by the different types of ligands on the receptor-controlled ion channel:

a) From the concentration dependence of channel activation it is concluded that at least two molecules of transmitter (or agonist) must be bound to the receptor to induce the opening of the integral ion channel. In equation (a) R,

$$R \overset{+A}{\rightleftharpoons} AR \overset{+A}{\rightleftharpoons} ARA \underset{\alpha}{\overset{\beta}{\rightleftharpoons}} (ARA)^* \qquad (a)$$

AR and ARA denote closed (inactive) states; (ARA)* denotes an open (active) state of the ion channel; k_β and k_α are the rate constants for the opening and closing of the channel (the mean open time is determined by k_α). Note that only the last reaction step is physiologically measurable and that data concerning the preceding steps can only be implied from physiological data.

b) Competitive blockers (antagonists) bind at the same sites as agonists, but cannot activate the ion channel ($k_\beta = 0$). They therefore hinder the activation of the channel by agonists [eq. (b)].

$$R \overset{+B}{\rightleftharpoons} BR \overset{+B}{\rightleftharpoons} BRB \qquad (b)$$

c) Non-competitive blockers (local anaesthetics) bind at their own binding sites at the receptor-ion channel already activated by agonists (open channel) [eq. (c)].

$$(ARA)^* + L \rightleftharpoons [(ARA)^*L] \qquad (c)$$

According to *Adams*[35] these binding sites are situated inside the channel, resulting in the following two consequences: firstly, occupation of these sites reduces channel conductivity (partial repolarization); secondly, the open state of the channel is stabilized or "frozen" (longer channel open time, k_α drops).

d) Other non-competitive blockers appear to act through binding to both the open and the closed channel or through binding to only the closed channel conformation[36].

In summary, the major effects of the different ligands on the receptor integral ion channel can be explained by the assumption of several states of the agonist-saturated receptor.

These are the inactive state ARA, the active state (ARA)*, and the modified active state [(ARA)*L]. Considering, however, that by electrophysiological methods several more open and closed states of the receptor channel can be distinguished[44-49], these models can only be a rough approximation of the true situation. The same conclusion can be drawn from a consideration of the structure of the various ligands (Fig. 3): 1) Considerable structural differences exist even within each class of cholinergic ligands. 2) The different affinities and reactivities of cholinergic ligands indicate that even ligands competing with each other probably do not bind to totally identical binding sites. The larger, more hydrophobic or more highly charged ligands have additional binding contacts with the receptor ("subsites"), or they bind to totally different bind-

ing sites with allosteric effects causing the observed competition. 3) The fact that the classification of the individual nicotinic ligands and also their relative potencies differ from one nicotinic system to the next also points to different and/or only partially overlapping points of attachment of the different ligands and the receptor.

This complicated situation is reflected in the models discussed for the interaction of ligands with neuroreceptors. As an alternative to the classical occupation model of pharmacology, in which binding of all ligands to identical binding sites is assumed, allosteric models were proposed rather early[70–74]. According to these, two ligands can still fully compete with each other (mutually exclusive binding), even if they bind to different binding sites. This can happen if binding of one ligand to its binding site alters the structure of the binding site for the other ligand so that its affinity of binding drops by several orders of magnitude[74]. The specific allosteric model[72,73] of *Monod* et al.[75] makes the additional postulate that different states (forms) of the receptor ion channel already exist *in the absence* of ligands, and that ligands merely shift the existing equilibrium of forms in favor of particular forms. Similarly to the other allosteric models, the specific allosteric model can also explain partial agonism in simple terms[76]. None of the existing models has as yet been proven. For a detailed discussion of the various approaches used to describe the dependence of activation on ligand concentration see [1,3,5,7,81,82].

4. Quantitative Pharmacological and Physiological Aspects

4.1. Dose-Response Relationships

These express the quantitative relationship between the magnitude of a physiological response and the concentration of a compound. They are the easier to interpret on a molecular basis the closer the effect under investigation is linked to the binding reaction. For instance, in the case of the cholinergic system, measurements of the changes in membrane conductivity (primary response) are preferable to measurements of muscle contraction (secondary response). Fundamentally, however, dose-response curves can only be interpreted in molecular terms *after* the underlying molecular mechanism—and thus when the true functional relationship between receptor saturation and response—has been established. In addition, there exist many experimental limitations in a system of such functional complexity. At higher concentrations of agonist, for instance, the phenomenon of desensitization becomes increasingly apparent. This is why potencies are often deter-

◀ Fig. 3. Structural formulas of typical ligands of the nicotinic acetylcholine receptor. In the case of salts, only the cations are shown.—a) Structure and favored conformation of the natural transmitter acetylcholine (ACh).—b) Structures of some nicotinic agonists of acetylcholine: **1**: carbamoylcholine, **2**: acetylthiocholine, **3**: thiocholine, **4**: substituted acetylcholines such as bromoacetylcholine (**4a**), acylcholines (**4b**) and "NBD-n-acylcholines" (trimethyl-2-[ω-(7-nitro-4-benzofurazanylamino)-*n*-alkylcarbonyloxy]ethylammonium ion, **4c**), **5**: sulfonium analogue of acetylcholine, **6**: nicotine, **7**: protonated cytisine [69], **8**: "bismethonium compounds" (hexamethyl-*N,N'*-polymethylenediammonium ions) with $n>6$, **9**: suberoyldicholine.—c) Structures of some nicotinic antagonists of acetylcholine: **10**: triethyl analogue of acetylcholine, **11**: acetylcholinamine, **12**: "bismethonium compounds" (hexamethyl-*N,N'*-oligomethylenediammonium ions) with $n\leq 6$, **13**: tubocurarine, **14**: trimethaphane, **15**: β-erythroidine, **16**: gallamine.

mined relative to a standard by comparing at relatively low concentrations (i.e. in a concentration range in which desensitization is negligible) the concentrations producing the same response.

Leaving aside their quantitative reliability, the dose-response curves have been found to be sigmoid in shape for all cholinergic agonists tested[51,77-79], and to yield Hill-coefficients of between 1.5 and 2[51,77,78] or 2.7[79]. Assuming simultaneous binding of the agonist molecules to the receptor, this would imply the presence of two or more agonist binding sites at the receptor with positively cooperative interactions between these sites. Alternatively, non-integer Hill coefficients[*] of less than 2 could be explained by an ordered binding of two agonist molecules to the receptor, since the related Hill plot would initially have a slope of 2, approaching a slope of 1 at very high agonist concentrations[80].

Any interpretation of Hill-coefficients on the basis of the number of binding sites at a receptor molecule implies that receptor saturation and induced response are directly proportional to each other. This is clearly not the case. For instance, all recent physiological data on the acetylcholine receptor-ion channel imply that it is activated only after *two* molecules of agonist have been bound. Thus, if one assumes direct proportionality only between the concentration of the fully saturated receptor (and not of the total number of binding sites) and the induced response, sigmoid dose-response curves could result even if no cooperativity exists between the two binding sites at the receptor[31,81,82]. Consequently, neither the shape of dose-response curves nor the size of the Hill coefficient are of much analytical value with respect to the molecular mechanism underlying the receptor-ligand interaction under study.

In contrast, the concentration of agonist at which half-maximal response is achieved is of important analytical value. Assuming that the response is directly proportional to saturation of both or of the second of the two binding sites per receptor molecule, this concentration is equal to the equilibrium dissociation constant for the saturation of the second binding site. Table 1 lists the half maximal concentrations and the Hill coefficients for some representative cholinergic ligands.

Table 1. Concentrations for half-maximal response and Hill coefficients of some cholinergic agonists [a].

Ligand	K_{app} [μM]	n	n_d
Acetylcholine	27.8	2.7	2
Carbamoylcholine	336	2.2	1.8
Suberoyldicholine	18	—	—
Nicotine	—	1.7	1.5

[a] After *Peper* et al. [79]. The data were obtained at room temperature on frog skeletal muscle fibers. K_{app}: concentration for half-maximal response; n, n_d: Hill coefficients, measured on normal and denervated muscle cell. For further K_{app} values see Table 3.

[*] The Hill coefficient is the slope of the middle, linear part of the curve obtained on plotting $\log z/(z_{00}-z)$ against $\log A$ where z, z_{00} and A denote the response z and maximal response z_{00} effected by the agonist concentration A.

4.2. Maximal Response

According to the classic occupation model[65], the response amplitude solely depends on the degree of receptor saturation, with all agonists therefore producing the same maximal response. This does not apply to the cholinergic system. For instance the maximal response to carbamoylcholine at frog muscle fibers is only about 80% of that to acetylcholine[79]. Agonists with smaller maximal response are called "partial agonists" (see Section 3) and are assumed to possess a smaller "intrinsic activity"[83] or "efficacy"[84] than agonists. *Ariens'* concept[83] keeps the direct relationship between receptor saturation and response and assigns an intrinsic activity of 1 to all full agonists. *Stephenson*[84] assumes that different ligands induce the maximal response by achieving different levels of receptor occupation. Other explanations for the differing maximal responses of agonists and for partial agonism appear to be equally plausible[10]. Consequently, direct studies of receptor-ligand interactions are required to establish the correct mechanism.

4.3. Chemical Modulation of the Response

When *Karlin* and *Bartels*[85] demonstrated in 1966 that the response of the electroplaque end plate to acetylcholine and a few agonists was greatly reduced after incubation with dithiothreitol (DTT) or *p*-chloromercuriobenzoate (PCMP), this was considered important evidence supporting the protein nature of the acetylcholine receptor. Later, it was shown[86,87] that DTT opens a specific disulfide bridge in the immediate vicinity of the binding site for acetylcholine at the receptor. This makes the freed SH-groups excellent targets for irreversible affinity labeling of the receptor—for instance with bromoacetylcholine or [4-(*N*-maleimido)benzyl]trimethylammonium iodide (MBTA). The reaction with DTT also changes the potency and/or the pharmacological classification of some of the cholinergic ligands tested[82,86-91]. For instance, the concentration of acetylcholine required for half-maximal response of the electroplaque cell of the electric eel is increased by approximately one order of magnitude and the cholinergic antagonist **8**, n = 6 (Fig. 3) is rendered an agonist. Equally noteworthy is the fact that many partial agonists are rendered full agonists of acetylcholine after treatment with DTT. The redox state of the disulfide bridges of the receptor also appears to be linked to the phenomenon of desensitization[92]. Chemical modifications at the specific disulfide bridge and their effects on the properties of the receptor have therefore become important tools in the biochemical analysis of the function of the receptor[82,90-95].

5. Biochemical Preparations and the Structure of the Acetylcholine Receptor

The biochemical characterization of nicotinic acetylcholine receptors began with *Lee*'s discovery of the antagonistic effect of the so-called α-toxins in the venoms of the snake family *Elapidae*[96]. These toxins (e.g. α-bungarotoxin, α-cobratoxin) bind with high affinity to and in particu-

lar dissociate extremely slowly from the receptor. They are therefore particularly suitable as affinity ligands. Initially even more important was the specificity of their action. In contrast to all low molecular weight antagonists (and agonists), they do not bind to acetylcholine esterase and, therefore, for the first time enabled unequivocal differentiation between the receptor and this synaptic enzyme. Meanwhile, binding sites for α-neurotoxins have been found in many tissues including the brain[91,97-102], the retina[103-105], sperm[106], and sympathetic ganglia[107] of mammals and other classes of animals[108-112]. In some systems these toxin binding proteins display similarities to the established nicotinic receptors[108,112-114], in others this is not quite as clear[115-117]. Of all the tissues from which acetylcholine receptors have been isolated in a pure form—the electric organs of the electric ray and the electric eel, various types of muscle tissue and cultivated muscle cells[118-131]—we shall limit ourselves here to the electric tissue. While from a medical and biological point of view the acetylcholine receptors of the brain and of mammalian muscle appear to be much more interesting, such larger amounts of receptor can be isolated from electric tissue that for almost all intensive biochemical studies this has been the source of choice.

The critical problem with every subcellular fractionation and purification of the acetylcholine receptor is the control of cellular protease activity. In particular, as SH- and Ca-activated proteases appear to be of importance in this connection[125,127,132,133]. If these are inhibited, sufficiently stable and structurally well defined receptor preparations can be obtained.

5.1. The Membrane-Bound Receptor

Using highly resolved autoradiography after labeling with radioactive α-toxin, the packing density of acetylcholine receptors in the region of the synapses has been shown to be much higher than in the extrasynaptic regions[134]. In synaptic regions the receptor density reaches 30000 molecules per μm^2[134,135], whereas only around 500 molecules per μm^2 are found in the extrasynaptic regions. Since the protein to lipid ratio is unusually high (>1.5)[136] in the subsynaptic regions, such membrane patches can easily be separated from other membrane fragments in density gradients after tissue homogenization. Receptor-rich membrane fragments from *Torpedo* electric organs obtained in this way already contain the receptor as the main protein component.

After removal of some peripheral proteins by alkaline treatment[137], the receptor in these membranes is finally concentrated to approximately 40—50%. Alkaline treatment leaves the fatty acid and phospholipid composition of the membranes largely unchanged[138]: The ratio of cholesterol to phospholipid is close to 0.4[139], that of phosphatidylcholine to phosphatidylethanolamine about 1[138-140]. The most striking result of the alkaline treatment is therefore the removal of a peripheral membrane protein (α', $M_r \approx 43000$) which is closely associated with the receptor and appears to have a structure-stabilizing effect[137,141-143]. After its removal, the receptor displays increased mobility in the membrane[94,163-165].

Electron micrographs after negative staining of such membranes from *Torpedo* show a high density of rosette-like structures (Fig. 4a) which are sometimes ordered in pseudohexagonal rows (not visible in Fig. 4). The doughnut- or horseshoe-like structures have a diameter of 7—9 nm with a heavily stained central pit of about 2 nm. Side views of negatively stained membranes and freeze-fracture experiments, show the receptor to project by about 5 nm on the extracellular side and by about 1.5 nm on the cytoplasmic side out of the membrane. By mathematical correlation and averaging over a large number of particles a structural model of the receptor (Fig. 4) has been developed from these data[143-153]. The results obtained are further supported by small angle X-ray scattering and neutron diffraction experiments[145,154]. From a large number of direct and indirect experiments it can be concluded that the observed ring structures are indeed acetylcholine receptors. Furthermore, it is clear that, at least at the present resolution of the experiments, no larger structural or functional changes have occurred in the receptor due to the use of contrast materials[155]. Raman spectroscopic studies[156] indicate a high content of α-helix structures in the receptor-rich membranes.

SDS gels of receptor-rich membrane fragments from *Torpedo* exhibit before alkaline treatment two, after alkaline treatment one major protein band and several minor bands corresponding to molecular weights of 40000 (43000), 50000, 60000; 68000 and 90000[132,140,157-161]. Of these the 43000-polypeptide is a peripheral membrane protein and the 90000-polypeptide a subunit of ATPase. Belonging to non-receptor proteins, these two bands are not observed in the gels of the purified receptor protein. With the help of selective proteolysis[172] and of antibodies[166,167] it has been shown that all four receptor polypeptides (subunits) protude the lipid membrane, while the 43000 non-receptor polypeptide is only accessible from the cytoplasmic side of the membrane[162].

Receptor-rich membrane fragments represent an unusually highly concentrated "natural" receptor preparation. They are particularly useful for studying the ligand interactions of the receptor (Section 6), the agonist induced changes in membrane conductivity[9], and ion-fluxes[2,6]. They therefore represent the simplest natural systems for the study of cholinergic excitation.

5.2. The Purified Receptor Protein

Being an integral membrane protein, the acetylcholine receptor protein is insoluble in water. It can only be kept dispersed in aqueous solution in association with detergents in the form of micelles. In order not to affect the binding function, non-ionic detergents are usually employed to disperse the receptor. It is common practice to use detergents with a low critical micelle concentration (cmc) for initial solubilization and to replace these by milder detergents during the purification procedure[118-120,125].

Typical purification procedures[125] begin with the homogenization of the electric organ in the presence of suitable protease inhibitors. The membrane fragments are then

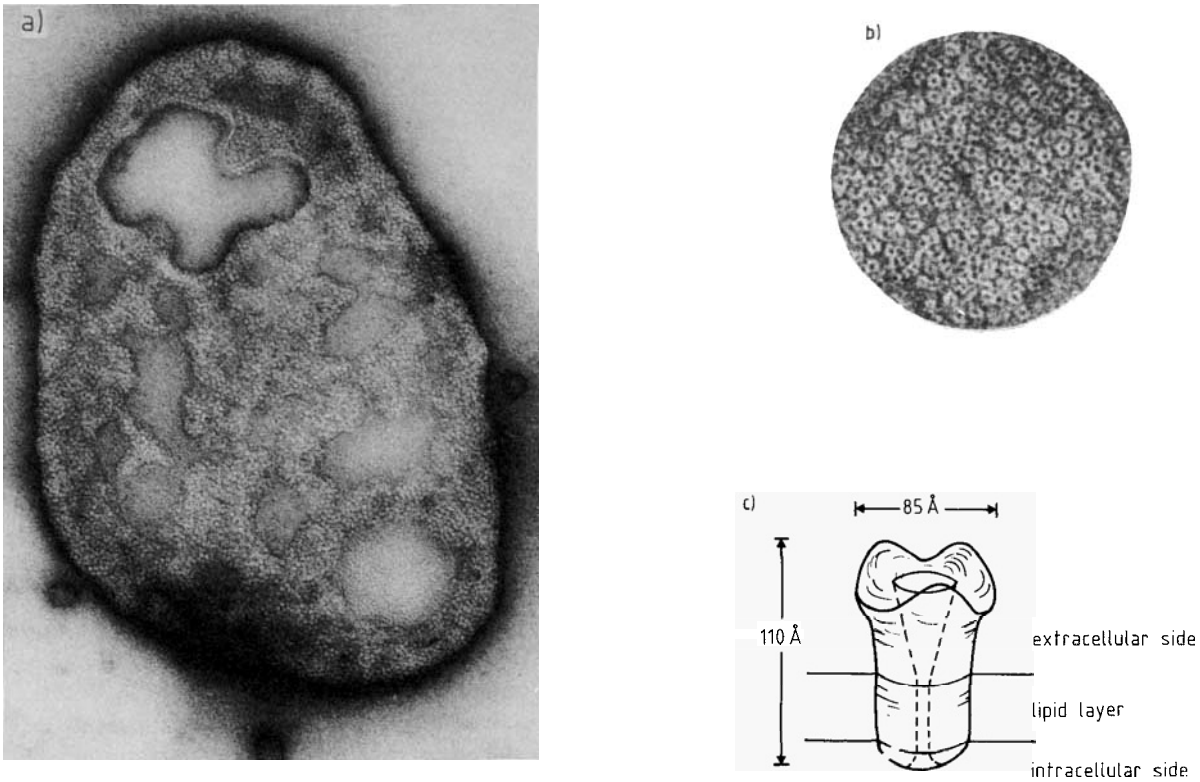


Fig. 4. a) Electron micrographs of receptor-rich membrane vesicles from *Torpedo marmorata*. Membrane vesicles in 20 mM phosphate buffer, pH 7.4 were negatively stained with 1% phosphotungstic acid of the same pH. Magnification ca. 85000 ×.—b) Enlarged section of (a).—c) Three-dimensional model of the acetylcholine receptor based on electron microscopic data. The electron micrograph was obtained by *S. Reinhardt*, Institut für Biochemie der Freien Universität Berlin [155]; the model has been drawn according to *Kistler* et al. [150].

centrifuged and "washed" several times in buffers of differing ionic strength. After removal by filtration of remaining connective tissue, the membrane suspension is incubated with a non-ionic detergent (final concentration 1%) and, after stirring for one hour, is centrifuged in the ultracentrifuge at about 50000 g for 2 hours. The solubilized receptor in the centrifuge supernatant can then be purified by affinity chromatography.

Several alternative procedures are available for affinity chromatography of the receptor: 1) The classical method uses α-neurotoxins as affinity ligands[118–120]. Because of their high affinities and low dissociation rate constants, the α-neurotoxins guarantee an optimal separation of the receptor from contaminating proteins including the acetylcholine esterase. The expected problem of the receptor being difficult to displace from the immobilized ligand owing to the small dissociation rate constants of these complexes does not apply because the dissociation rate of receptor-toxin complexes is accelerated by several orders of magnitude in the presence of higher concentrations of low molecular weight ligands[74, 168, 169]. 2) Since their complexes with the receptor dissociate very rapidly, ligands of low molecular weight are less suitable as affinity ligands. While the stability of their complexes with the receptor appears to increase after immobilization, such affinity columns can not be washed as rigorously as is common practice for toxin affinity columns. Consequently, low molecular weight affinity ligands have proved useful only for preparations which do not require a large enrichment of the receptor[170]. 3) As reversible ligands, monoclonal antibodies against the receptor protein[159, 171–176] are also potentially suitable for the purification of the receptor. Because of the success of the previously mentioned methods, however, they have not yet found broad application with this particular receptor system[177]. 4) Since the receptor is a glycoprotein with significant affinity for certain plant lectins[120, 121, 178–181] it can also be purified by means of immobilized lectins. Such affinity columns, however, have only found application as a second step of the purification procedure and with questionable success[121].

The classical purification procedure by means of toxin affinity columns[119–125, 168] uses α-cobratoxin immobilized on CNBr-activated Sepharose. In order to facilitate the dissociation of the biospecifically adsorbed receptor from the affinity gel, gels of low toxin binding capacity are employed[125, 168]. In this way it is avoided that the majority of receptor molecules is bound to more than one toxin molecule at the gel matrix which would dramatically decrease the probability of dissociation[182]. Affinity gel and membrane extract are mixed slowly with stirring for several hours, and the column is then washed with different buffers. After all contaminating protein is washed out, the receptor is eluted with an antagonist-containing buffer (0.005–0.1 M **8**, $n = 6$[125, 168]). The receptor-containing eluate is applied to a column (hydroxyapatite[119]) whose gel binds the receptor but not the ligand employed for affinity elution. The receptor-free ligand solution is then recycled to the affinity column[119] for further competitive

displacement of the receptor from the affinity matrix. When after a few hours the receptor is completely eluted from the toxin column and bound to the hydroxyapatite column, the latter is disconnected and washed. Finally the receptor is eluted from the hydroxyapatite column with phosphate buffer. In this way 30–100 mg of pure receptor protein can be obtained from 1 kg of the electric organ of *Torpedo*[125]. Employing the standard method the purified receptor protein is contaminated with less than 0.1% of esterase activity[125].

As shown by electrophoresis, isoelectric focussing, sedimentation in density gradients, equilibrium sedimentation studies, and laser light scattering[125, 183–185], the purified receptor is obtained as a mixture of monomers and dimers (Fig. 5). Treatment with disulfide reducing agents or with high concentrations of certain non-ionic detergents completely converts the dimers into receptor monomers[125, 157, 160, 186–189]. Preparations from the electric ray *(Torpedo)* contain much higher concentrations of dimer than those of the electric eel *(Electrophorus)* under the same experimental conditions[125].

The existence of two forms each of the receptor monomer and the receptor dimer from *Torpedo* (Fig. 5, [125]) suggests that the receptor can exist in non-globular forms in solution. These different forms of the receptor appear to be in equilibrium with each other and to be dependent on the nature and concentration of the bound detergent and also on the redox state of some cystein residues (Fig. 5). This multiplicity of forms may have been responsible for the perennial controversies surrounding the hydrodynamic properties and the molecular weight of the receptor[1, 2, 4].

At present the following data seem to be established. The receptor from *Electrophorus* (mostly monomer, see Fig. 5, [125]) dissolved in non-ionic detergent has a Stoke radius of 7 nm[119, 120, 190], the monomer and dimer from *Torpedo* receptor Stoke radii of 7 nm and 8.5 nm, respectively[191, 192]. By measurement of sucrose gradients[193] or sedimentation rates[125], a sedimentation coefficient of about 9 S is found for the eel receptor and of 9.3 and 14.4 S, respectively, for the monomer and dimer from *Torpedo*. Monomer and dimer do not spontaneously interconvert and, therefore, can be investigated separately after separation in density gradients. In this way, ultracentrifuge studies employing the density matching procedure of *Tanford*[194, 195] yielded a molecular weight of $250\,000 \pm 7000$[196] or $275\,000 \pm 15\,000$[125, 185] for the receptor monomer from *Torpedo*. For the receptor monomer from *Electrophorus* a molecular weight of $262\,000 \pm 12\,000$ has been obtained with the ultracentrifuge and of $287\,000 \pm 8000$ by means of laser light scattering[125, 185]. From the known amino acid sequences of all subunits of the *Torpedo* receptor[197–201] and assuming a subunit composition of $\alpha_2\beta\gamma\delta$[202], a molecular weight for the monomer of 268 000 can be calculated. From the translational diffusion coefficient $D_{20,w} = 2.95 \times 10^{-7}$ cm^2 s^{-1} and the sedimentation coefficient $S_{20,w} = 9.29$[125], the ratio of the friction coefficients f/f_0 is calculated as 1.51[*], indicating considerable structural asymmetry of the receptor monomer from *Torpedo* when dissolved in low concentrations of detergent (0.05% Tween

[*] f_0 is the friction coefficient of a spherical object; f/f_0 is therefore a measure of the deviation from sphericity.

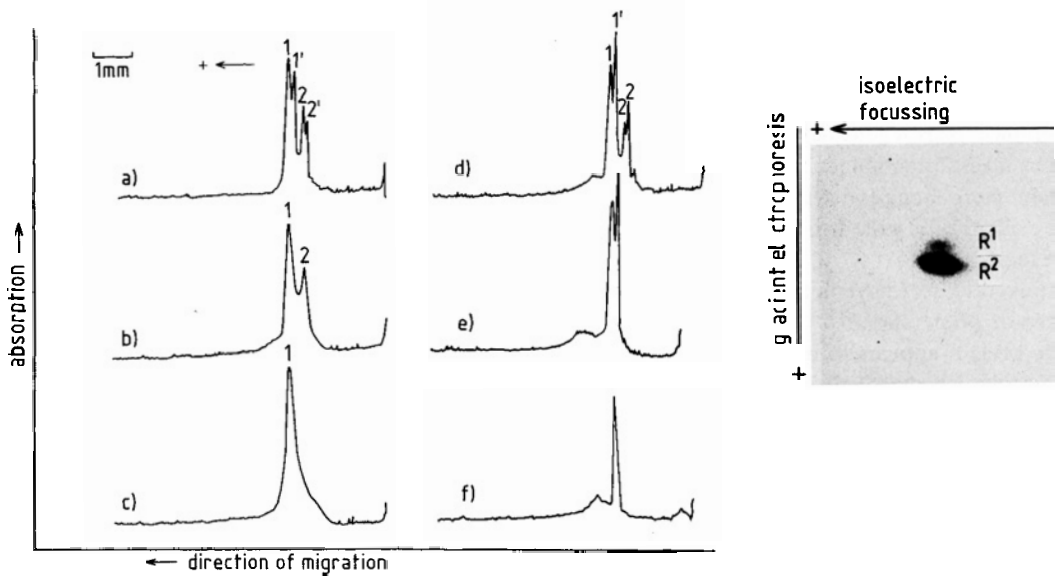


Fig. 5. Gel electrophoresis of the purified acetylcholine receptor from *Torpedo marmorata* under different conditions.—(Left): The receptor was subjected to anodic electrophoresis in the presence of a) 0.1% octylglucoside, b) 20 mM dithiothreitol and c) 20 mM dithiothreitol with 1% Triton X-100. Under non-denaturing conditions in low concentrations of a mild detergent (a), the receptor exists in two forms each of the monomer (1,1') and of the dimer (2,2'). By treatment with disulfide-reducing agents (b), the two dimeric forms are completely converted into the monomeric forms. The two monomeric forms are completely interconvertible if the properties of the receptor-detergent micelle are correspondingly changed through changes in the concentration or type of the detergent (c).—(Middle): Anodic electrophoresis in cylindrical gradient microgels of the purified *Torpedo* receptor in the presence of (d) 0.05% Tween 80, (e) 0.4% Triton X-100 and (f) 2% Triton X-100. In comparison to the experiments described on the left, it is shown that the conversion of dimers into monomers and of the two monomers into a single monomer can also be achieved by non-ionic detergents alone.—(Right): Two-dimensional microelectrophoresis of the acetylcholine receptor from *Electrophorus electricus* and labeling of the bands with ^{125}I-α-bungarotoxin. Two receptor-toxin complexes differing in their size but not in their isoelectric point are observed [125].

80). The relatively low values of $D_{20,w}$ and $S_{20,w}$ for a molecule of this size also point to a relatively loose (e.g. partially unfolded) structure of the receptor in solution.

Comparing the apparent molecular weights of the receptor subunits as obtained by SDS-polyacrylamide gel electrophoresis with the exact data from the protein sequences[197-201], the electrophoretic method turns out to be rather unreliable for this integral membrane protein. From SDS gel electrophoresis the following apparent molecular weights for the subunits (exact values from gene sequencing in brackets) have been obtained: 40000 (50200), 50000 (53681), 60000 (56279), and 67000 (57565). Accordingly, the typical band pattern of the receptor[68, 87, 120, 121, 123, 136, 140, 179, 183, 186, 203, 204] is due to an electrophoretic artifact resulting from either differing affinities for detergent or differences in form and or packing densities of the subunits. The same artificial separation is also observed after cross-linking the subunits with bifunctional reagents[203,204], a technique believed to permit complete introduction of membrane proteins into SDS-micelles. It is therefore unlikely that the erroneous apparent molecular weights of the subunits are due to the use of water-soluble proteins as molecular weight standards[205]. Thus, the irregular deviations from the exact values probably reflect structural differences of the SDS-denatured subunits.

The strong influence of the surrounding detergent—and by inference the surrounding lipids in the membrane-bound state—on the structure of the receptor is also reflected by the fact that *Torpedo* receptor dimers can be converted into monomers merely by the presence of higher concentrations of certain non-ionic detergents (Fig. 5[125,157,205-207]). This implies that the disulfide bridges connecting the δ-subunits of dimers[186-188] can be cleaved *without* external disulfide-reducing reagents. The detergent-induced opening of the δ-δ-disulfide bridge requires, however, the existence of free SH-groups in the receptor structure[125]. Hence, cleavage of this disulfide bridge is probably not a reduction but a rearrangement of disulfide and SH-groups induced by a conformational change of the receptor to accommodate more bound detergent molecules. This is additional evidence for wide structural flexibility of the receptor protein.

Since only δ-subunit linked dimers have been found in the various *Torpedo* receptor preparations[186-188], the formation of these disulfide bridges appears to be a specific event. It is not clear, however, whether their formation is caused by the lattice-like arrangement of receptor molecules in the subsynaptic area[151,152] or whether the presence of certain accompanying membrane components is required[186]. In contrast, cleavage of the disulfide bridges does not appear to require[125] the presence of the postulated[186,187] special membrane component—"a protein that contains SH-groups with unusually low redox potential and with close proximity to the receptor"[186]. Cleavage and re-formation of the disulfide bridge therefore varies with the reaction conditions and can lead to different results[187,189].

It has been postulated that the dimer represents the biologically active form of the receptor[187]. Accordingly, the high content of monomers observed in most preparations of purified receptor[118-131] would have to be the result of side reactions during solubilization of the receptor (caused, e.g., by the exposure of intramolecular SH-groups[188]—about 25% of the receptor's cysteines are free, the others form disulfides[186,188]). Physiological, biochemical and reconstitution experiments[12,14,82,85,90,91], however, contradict this hypothesis; at present only minor if any modulations of receptor properties due to dimer formation appear to be likely. A quantitative comparison of the properties of receptor monomers and dimers has as yet only been carried out for the interaction with α-cobratoxin[125]. For this reaction no fundamental differences were detected.

The purified receptor has a relatively low isoelectric point of $pH_I \approx 5$[118,208,209], with small differences between synaptic and extrasynaptic receptors[210]. All subunits of the receptor are glycoproteins and therefore bind to concanavalin A and other plant lectins[120,162,179,210-212].

While protein sequencing of the receptor subunits has advanced only very slowly[201,213,214], cloning of the genes of all subunits of the *Torpedo* receptor[197-201] and the α-subunits of the calf and human muscle receptors[215] has yielded the complete sequences of these. With these at hand, many basic problems concerning the structure and function of the acetylcholine receptor can be analyzed in quantitative molecular terms. These include the exact sequence positions of the ligand binding sites, of the integral ion channel, of the disulfide bridge near the binding sites for agonists and the positions for phosphorylation[216-223], *N*-glycosylation[224], and methylation[225].

On the basis of the sequence data for the *Torpedo* receptor, hydrophobicity profiles[226] have been calculated and secondary structures[227] postulated. According to these, every subunit of *Torpedo* receptor contains four sequence segments which protrude the membrane and, therefore, could take part in the formation of the receptor-integral ion channel[197,200,201,215]. The strong sequence homologies between the α-subunits of *Torpedo*, calf and human receptors suggest that all these receptors are built into the surrounding membrane according to the same structural principles[215].

Because of the absence of a compartment border, ion fluxes and other electrical responses cannot be measured with solubilized receptor. These preparations are therefore limited to the study of such properties of the receptor that solely require an intact protein structure and do not depend on the membrane potential or the existence of ion gradients. Under these conditions studies with the purified receptor can reach an accuracy comparable with that of biochemical studies of water-soluble proteins such as enzymes.

5.3. The Reconstituted Receptor

Initially, the acetylcholine receptor was purified only as a binding protein for cholinergic ligands[118-132]. This also complied with the classical pharmacological concept of the receptor as specific binding site[62-64]. It was then shown by the reconstitution experiments described below that the affinity-purified receptor molecule not only con-

tains the binding sites for agonists but also the ion channel controlled by these[12]. Reconstitution experiments, therefore, are of fundamental conceptional value. More recently, they have also become useful preparations in the study of the effects of membrane structure and composition on the properties of the receptor and its integral ion channel.

Basically, reconstitution of the acetylcholine receptor is defined as the reincorporation of the purified receptor protein into a lipid membrane and the positive proof of agonist-dependent changes in its electrical conductivity. More stringently defined, a properly reconstituted cholinergic system must display the same single channel characteristics as those typical for natural end plates including pharmacological specificity. The crucial problem then is to define the minimal system still capable of displaying these properties.

The first reconstitution experiments[183,228-240] were aimed at obtaining preparations with similar properties as natural membrane vesicles in order to employ them in ion flux studies[228,241,242]. For this purpose, the solubilized and purified receptor was mixed with artificial lipid vesicles and the detergent removed by dialysis or filtration. These membranes vesicles were then charged with radioactively labeled cations and the discharge kinetics were measured in the presence and absence of cholinergic ligands. Although these methods have only recently reached the time-resolution of physiological events[243,244], the earlier studies already suggested that incorporation of purified receptor protein into artificial membranes leads to a functional ion translocation system with specifically cholinergic pharmacology. These earlier studies, however, were largely qualitative in nature and, therefore, were not capable of establishing the similarities and differences between the reconstituted and the natural system. They demonstrated, however, that the 43000-peptide (cf. Section 5.1) of receptor-rich *Torpedo* membranes initially proposed to contain the ion-channel[141] was not required for ion translocation and that the ion channel is also not a protein component which can be separated from the receptor under non-denaturing conditions. Recent reconstitution experiments[238] could not confirm the claim from earlier studies[244] that the receptor dimer is the only biologically active conformation of the receptor[187].

The receptor has also been reconstituted into planar lipid bilayers according to the methods of *Mueller* et al.[245] and *Montal* and *Mueller*[246]. Using this technique, the first single channel recordings from reconstituted purified receptor protein were obtained[12]. Since at the time of these investigations single channel recordings from intact electroplax cells had not yet been obtained, receptor-rich membrane fragments from *Torpedo* were first incorporated into the artificial lipid bilayers and their electrical properties were compared with those of muscle endplates from rat and frog (Fig. 6). The characteristic, agonist-induced single channel events recorded on the implanted membrane fragments then served as a standard for the reconstitution of purified receptor protein. These experiments showed that the receptor protein purified by affinity chromatography, already as monomer provided the artificial membrane with the electrical properties typical for natural end plates. Therefore, the agonist activated ion-channel

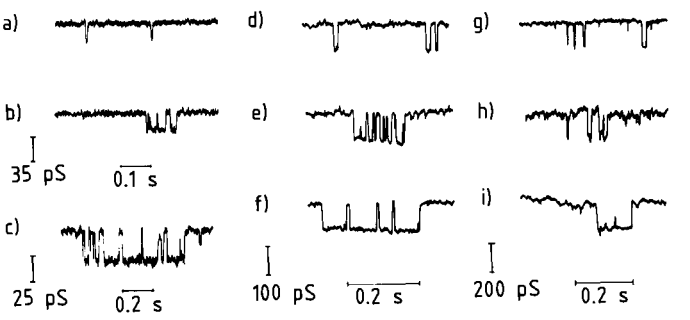


Fig. 6. Acetylcholine-induced single channel events in natural and reconstituted membranes containing acetylcholine receptor [12]. The scale 35 pS/0.1 s applies for a) and b), the scale 100 pS/0.2 s for d)—f) and the scale 200 pS/0.2 s for g)—i). Traces a, b, c show acetylcholine-induced membrane currents recorded with the patch-clamp technique [33] from extrasynaptic membrane regions of chronically denervated rat muscle (a, b) or frog muscle fibers (c): a) Single channel events immediately following addition of acetylcholine; b) multiple channel openings observed after longer incubation times on the same patch of membrane; c) infrequently occurring complicated events ("bursts"), believed to be events of resensitization of single channels. Traces d, e, f are obtained from an SMPC bilayer into which alkaline-treated receptor-rich membrane fragments from *Torpedo marmorata* were incorporated. Traces g, h, i are obtained from an SMPC bilayer into which purified receptor protein was incorporated. Very similar excitation patterns were observed for the natural membrane (a—c), the partially purified *Torpedo* membrane (d—f) and the reconstituted system (g—i).

had to be an integral part of the receptor protein. This is in agreement with recent results published by other groups[13,14,247,248].

The reconstitution experiments of *Boheim* et al.[12,249] are particularly noteworthy for their use of a phospholipid—1-stearoyl-3-myristoylglycero-2-phosphocholine (SMPC)[250]—with unusually high phase transition temperature[251]. Using this lipid the reconstitution of the receptor could be studied under conditions of a frozen membrane matrix. Since the reconstituted system functioned normally under these conditions (Fig. 6[12]), the lipid membrane apparently only functions as compartment border and, therefore, is not required to possess any great fluidity. Thus, the electrical properties of the reconstituted system—and by inference also those of natural muscle end plates—are properties solely of the protein moiety of the receptor. (This is not yet fully established, however, because at present it cannot be ruled out that the purified receptor protein still contains a few tightly bound molecules of natural phospholipids[252].) In any case it is clear, however, that the purified receptor monomer and dimer can function similarly to natural end plates when incorporated into bilayers of an artificial phospholipid. This also proves that solubilization and isolation of the receptor protein can indeed take place without loss of function and that the solubilized receptor therefore represents an intact, i.e., functional receptor preparation[253]. Furthermore, it disproves earlier suggestions that the purified receptor is a desensitized preparation.

Recently[14], single channel recordings have also been obtained from receptor reconstituted into a lipid bilayer at the tip of a pipette[32,33,254] (see Fig. 2a). In this way, and independent of the agonist applied, single channel conductivities of 40 ± 5 pS were measured in a medium containing 0.5 M NaCl; furthermore, two discrete types of single channel events and the typical sequence of events in the course of desensitization were observed[14].

The recently developed reconstituted receptor systems[12-14,249] are noteworthy for their stability and reproducibility. Since they can be biochemically manipulated rather easily (the lipid and protein composition, the relative proportions of monomer and dimer, the structure of the receptor can all be varied), they are particularly useful in connection with the purified receptor for the analysis of cholinergic mechanisms. Since natural membrane vesicles from *Torpedo* have recently become accessible to the patch-clamp method[255,256], there exists an unusual variety of receptor preparations for both biochemical and physiological studies. These (the highly purified receptor protein, the various reconstituted systems, partially purified membrane vesicles, and whole subsynaptic membranes) offer unique possibilities to study the molecular principles of biological signal processes.

6. Interaction of the Acetylcholine Receptor with its Ligands

6.1. Binding Studies

In this section we shall restrict ourselves to the discussion of binding studies only, i.e. we shall for the moment disregard the effects ligand binding may excert on the ion channel. In the same way, however, as response measurements permit implications about the preceding binding steps (see Sections 2 and 4), the biochemical experiments described here permit implications about the accompanying or following activation steps of the receptor-integral ion channel. The central aim of any investigations of the mechanism of cholinergic excitation must be an understanding on the molecular level not only of the binding reaction but also of channel activation and the coupling between these two processes.

Independent of the pharmacological classification of the ligands of the acetylcholine receptors (Section 3), we shall consider them here on the basis of their biochemical properties:

1. Reversible Ligands of low molecular weight: Several hundreds of such ligands (Fig. 3) are known for the receptor. They typically possess relatively large rate constants of association and dissociation and, therefore, are particularly useful for functional studies.
2. Irreversible Ligands of low molecular weight: These are particularly useful for fixing a structure or a state of the receptor.
3. Neurotoxins: These are single chain polypeptides, occurring in the venoms of elapid snakes. They typically possess very high affinities for and extremely slowly dissociate from the receptor. They constitute the most specific ligands of the receptor, and, therefore, are most useful as specific marker molecules, for concentration determinations, and for affinity chromatography.
4. Antibodies: Within the framework of biochemical investigations of the receptor, these ligands are most useful for investigations of receptor structure and membrane topography. By clonal selection of the cells producing a particular (monospecific) antibody it now is possible to obtain specific marker molecules for every antigenic determinant at the surface of the receptor.

6.1.1. *Neurotoxins*

Polypeptide neurotoxins[96,257,258] are small basic proteins with a chain length of between 60 and 75 amino acids. The "short" neurotoxins possess four, the "long" five disulfide bridges. Besides the amino acid sequences of more than 100 neurotoxins, the X-ray structures of two long toxins[259,260] (Fig. 7) and one short toxin are known[261,262].

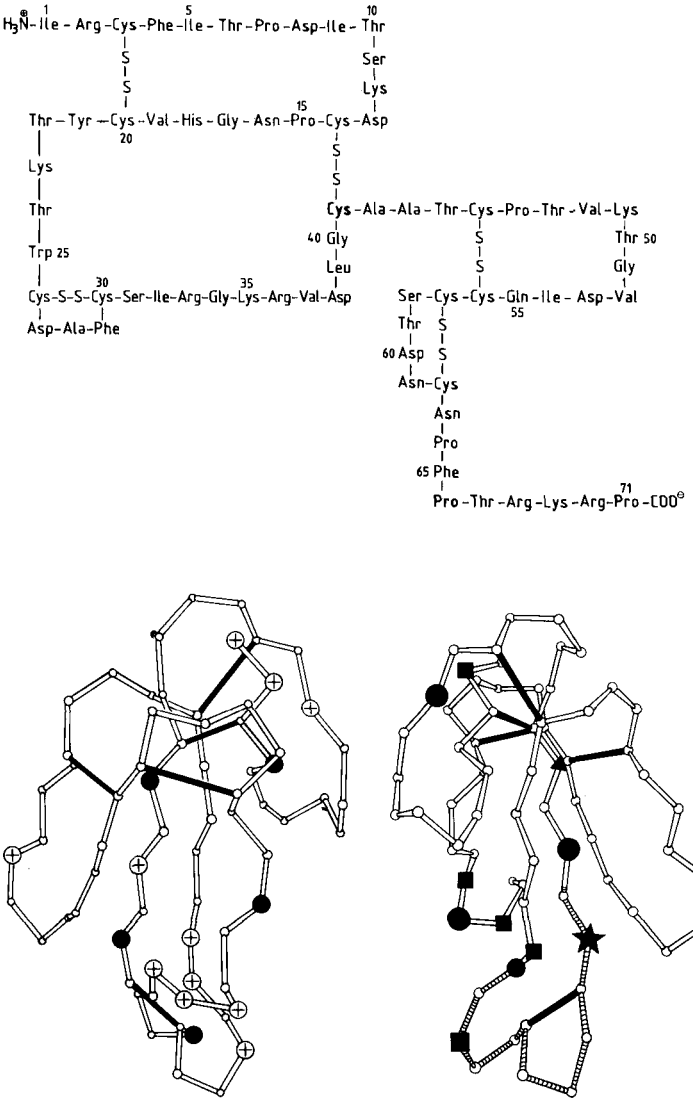


Fig. 7. The structure of α-cobratoxin.—(Above): Amino acid sequence of α-cobratoxin.—(Below, left): Back side view of the three-dimensional structure of α-cobratoxin with the positions of the aromatic (●) and the positively charged (⊕) amino acids indicated.—(Below, right): Front side view of α-cobratoxin with the positions of the amino acids modified by *Martin* et al. [263] indicated: Lysine (●), arginine (■), tyrosine (▲), tryptophan (★). Neither the modification of all lysine residues nor of all arginine residues or of the single tryptophan can completely abolish the toxicity of α-cobratoxin. Even after all five disulfide bridges have been opened and the free SH-groups alkylated, there still remains some residual toxicity. The peptide fragments from the region around the extra disulfide bridge (dotted line in the illustration below, right) also possess some residual toxicity [270—272]. Experimental details see [263, 264]; for a detailed discussion of the three-dimensional structure of α-cobratoxin see [259, 268, 269].

Neurotoxins bind by several attachment points to the receptor, i.e. they do not contain a narrowly defined active site[263,264]. The dissociation of the toxin-receptor complex is unusually slow[168,266,267].

Neurotoxins are easy to purify[96,168,257,258,263,273], to label with radioactive[168,273–276] or fluorescent residues[74,163,277–279], and to couple irreversibly with other proteins[280]. Since toxins are very basic proteins and the acetylcholine receptor is an acidic protein, simple analytical separation procedures can be developed on the basis of filters coated with ion-exchange resins[168,266,267,276]. For instance, filters coated with anion exchanger retain the receptor and the receptor-toxin complexes thereby permitting the determination of the concentration of these complexes. Because of the extremely slow dissociation rates of toxin-receptor complexes, the separation from free toxin can be carried out so completely that high accuracy and reproducibility can be achieved[168,276,281].

As was shown for purified acetylcholine receptor from electric eel and for ^{3}H-labeled α-cobratoxin[168,169,276], the interaction of receptor and neurotoxin cannot be described by one forward and one reverse reaction. Instead, two complexes of different affinity ($K_{D1}=4\times10^{-10}$ M, $K_{D2}=2\times10^{-11}$ M) and dissociation rate constants ($k_1=3\times10^{-3}$ min^{-1}, $k_3=1\times10^{-4}$ min^{-1}) are formed and these can isomerize with each other[168]. The interaction between receptor and toxin is characterized by an unusually high positive reaction entropy ($\Delta S_{298}=99$ cal·mol^{-1} K^{-1}); the activation enthalpy of the forward reaction ($\Delta H^{+}=12$ kcal/mol) is not unusual[168].

The toxin-binding test can also be employed for the study of the binding equilibria between receptor and low molecular weight ligands. Such competition binding studies already showed[168] that the purified receptor protein is capable of discriminating between pharmacologically distinct ligands: Cholinergic agonists and antagonists bind to the same number of binding sites at the receptor in a mutually exclusive fashion. However, antagonists are bound to these sites with only a single affinity, whereas agonists are bound with concentration-dependent affinity indicative of negatively cooperative interactions between pairs of sites (Fig. 8). The competition constants (Tables 2 and 3) for antagonists are in good agreement with the blocking potency in-vivo while for agonists differences of several orders of magnitude to the concentrations for half-maximal response are commonly found. This is not too surprising since the long incubation periods of the equilibrium binding experiment should lead to desensitization of the receptor if agonists are present[12,18,44,50–56].

Two of the observations made by *Maelicke* et al.[168] deserve special attention: In the case of the bismethonium compounds **8**, n=4 to n=10 (cf. Fig. 3), a single class of binding sites was found for the members with n=4—6, and heterogeneous binding (negative cooperativity) for the larger members. This is in agreement with the pharmacological classification of these compounds and demonstrates the sensitivity in response to small differences in ligand structure of the receptor protein. The second unusual observation has to do with the effect of low molecular weight ligands on the dissociation rate of toxin-receptor complexes. Assuming mutually exclusive binding, the added small ligand should only affect the equilibrium concentrations of receptor-toxin complexes but not their kinetics of dissociation. On the contrary, however, (Fig. 9a[74,168,169]) small ligands can accelerate this dissociation several hundredfold. Since the effect is observed only at very high concentrations (much beyond the concentration range used in the competition studies with toxin), yet is saturable, available binding sites for small ligands even in the presence of "saturating" concentrations of toxin are indicated. These show up in the kinetic but not in the equilibrium binding experiments[168]. Thus, the effect probably

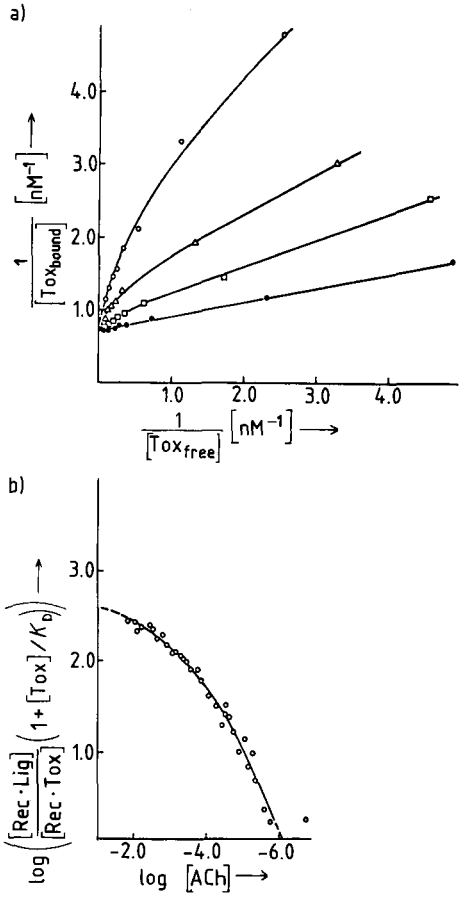


Fig. 8. Competitive binding of ^{3}H-α-cobratoxin and acetylcholine to the purified receptor protein from *Electrophorus* [168]. a) Double reciprocal plot of the concentrations of bound and free toxin. Acetylcholine concentrations: (●) 0, (□) 4.1×10^{-5} M, (△) 2.0×10^{-4} M, (○) 7.5×10^{-4} M.—b) Logarithmic plot according to *Maelicke* et al. [168]: Concentrations of receptor (Rec) and toxin (Tox): $[Rec_0]=1.9\times10^{-9}$ M, $[Tox_0]=2.7\times10^{-8}$ M, sample volume 1.04 mL. All reactions were carried out in the presence of 1.1×10^{-3} M diisopropylfluorophosphate, an inhibitor of acetylcholinesterase. From the initial slope (m=0.95), the same number of competitive binding sites appear to exist for toxin and acetylcholine. Competition constants of the initial binding site $K_{Lig}=7.9\times10^{-7}$ M. The complete functional relationship is as follows:

$$\log\left(\frac{[Rec\cdot Lig]}{[Rec\cdot Tox]}\left(1+\frac{[Tox]}{K_D}\right)\right)=n\log[Lig]-n\log K_{Lig}$$

with [Rec], [Tox] and [Lig] denoting the molar concentrations of toxin binding sites (receptor), toxin, and competitive ligand, respectively, in mol/L. n denotes the ratio of binding sites of the competitive ligand and toxin. K_D is the equilibrium dissociation constant of the toxin-receptor complex, K_{Lig} the apparent inhibition constant for the competitive ligand. Under the experimental conditions used, the concentration of free receptor can be neglected, so that the total concentration of binding sites. [Rec_0] equals the sum of the complexed binding sites ([Rec_0]=[Rec·Lig]+[Rec·Tox]). Thus, all quantities are experimentally accessible.

Table 2. Equilibrium dissociation constants of nicotinic ligands with the purified acetylcholine receptor (see also Fig. 8).

Ligand	Receptor from *Electrophorus*			Receptor from *Torpedo*	
	K_{Lig} [M] [a]	K_{Lig} [M] [b]	K_{Lig} [M] [b]	K_D, K_{Lig} [M] [c]	K_{Lig} [M] [d]
Acetylcholine	8×10^{-7}	1×10^{-7}	2×10^{-6}	6×10^{-8}	2.5×10^{-6}
Carbamoylcholine	7×10^{-7}	4×10^{-6}	6×10^{-5}	1×10^{-6}	4.5×10^{-6}
Nicotine	1×10^{-7}	—	—	1×10^{-6}	8×10^{-5}
8, n = 10	6×10^{-9}	1×10^{-8}	6×10^{-7}	2×10^{-8}	2×10^{-6}
Tubocurarine	1×10^{-7}	3×10^{-7}	2×10^{-7}	2×10^{-7}	1×10^{-7}
Gallamine	—	5×10^{-8}	1×10^{-7}	1×10^{-7}	2×10^{-7}
Benzoquinonium ion	6×10^{-8}	—	—	—	—
Alloferine	9×10^{-10}	—	—	—	—
8, n = 6	4×10^{-6}	2×10^{-5}	2×10^{-5}	7×10^{-5}	2×10^{-6}

[a] Obtained by competition binding studies with ^{3}H-α-cobratoxin (Filter test, [168]). [b] Competition binding studies with NBD-5-acylcholine (fluorescence binding studies [82]). [c] Obtained by equilibrium dialysis; direct measurement for acetylcholine and **8**, n = 10, otherwise competition studies [120]. [d] Equilibrium dialysis [411].—In [a] and [b] more than one class of binding sites have been observed, only in [82] have two K_D values been calculated.

Table 3. Equilibrium dissociation constants of nicotinic ligands with the membrane-bound acetylcholine receptor.

Ligand	Receptor from *Electrophorus*				Rezeptor from *Torpedo*	
	K_{app} [M] [a]	K_{app} [M] [b]	K_p [M] [c]	K_{app} [M] [d]	K_p [M] [e]	K_p [M] [f]
Acetylcholine	1×10^{-6}	—	2×10^{-6}	1×10^{-7}	6×10^{-9}	8×10^{-9}
Carbamoylcholine	3×10^{-6}	4×10^{-5}	4×10^{-5}	3×10^{-5}	4×10^{-8}	5×10^{-7}
8, n = 10	1×10^{-6}	1×10^{-6}	8×10^{-7}	2.5×10^{-6}	9×10^{-9}	8×10^{-7}
Trimethyl(phenyl)ammonium ion	1×10^{-5}	—	—	—	—	—
Tubocurarine	2×10^{-7}	2×10^{-7}	2×10^{-7}	2×10^{-7}	3×10^{-8}	2×10^{-7}
Gallamine	3×10^{-7}	4×10^{-7}	3×10^{-7}	5×10^{-6}	8×10^{-8}	1×10^{-5}
8, n = 6	3×10^{-5}	6×10^{-5}	6×10^{-5}	2×10^{-6}	5×10^{-7}	4×10^{-5}

[a] Electrophysiological dose-response curves [406]. [b] ^{22}Na flow from membrane vesicles [241]. [c] 50% decrease in initial rate of association of ^{3}H-cobratoxin with the receptor [287]. [d] From dose-response curves [406]. [e] 50% decrease in initial rate of association of ^{125}I-α-bungarotoxin with the receptor [411]. [f] By ultracentrifugation or decrease in initial rate of association of ^{3}H-cobratoxin with the receptor [287].

involves the same binding sites which in the low concentration range are competitive with toxin binding. This implies that structurally distinct binding sites for toxin and the small ligands must exist, and that competition of these ligands is not brought about by mutually exclusive binding to identical sites but is due to allosteric effects (Fig. 9b, see also Section 3). Independently of their structural basis, these low affinity binding sites possess the typical properties of additional regulatory sites[74, 168, 282–285].

Employing radioactively labeled toxins, ligand binding studies have also been performed with other preparations of the purified receptor[93, 286], with membrane vesicles[178, 179, 287–291], and with whole cells[292–298]. In the latter case they were employed in studies of the metabolism of acetylcholine receptors under normal[296, 297] and pathological conditions[298].

6.1.2. *Radioactively Labeled Small Ligands*

These ligands have mainly been used for equilibrium binding studies[137, 186, 230, 299, 304]. Because of their low affinity for the receptor in comparison to the neurotoxins, much higher concentrations of receptor are needed for these experiments. Consequently most of the studies with these ligands have employed receptor-rich membrane fragments from *Torpedo*. Of the methods used—equilibrium dialysis, filtration, centrifugation—only the latter has proved to be dependable. Ultracentrifugation in the airfuge[299, 301] to separate particulate from solute phase is an equilibrium method with comparatively good time-solu-

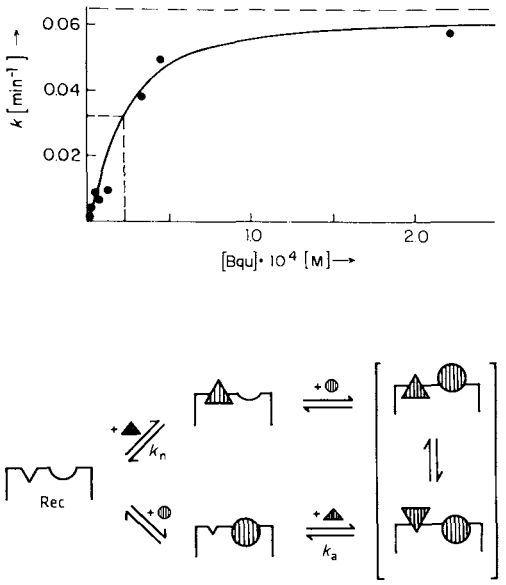


Fig. 9. Accelerated dissociation of toxin-receptor complexes. (Above): Initial rate constants of dissociation of ^{3}H-toxin-receptor complexes in the presence of the cholinergic antagonist benzoquinonium (Bqu).—$k_{max} = 0.065$ min^{-1}, $c(1/2k_{max}) = 2.4\times10^{-5}$ M [168]. Under similar conditions, $c(1/2k_{max})$ values of 1.1×10^{-4} M and 5×10^{-2} M, respectively, were found for tubocurarine and carbamoylcholine [74].—(Below): Allosteric model of accelerated dissociation. The binding sites for toxin and the small ligands are considered to be non-identical but fully competitive over a wide range of ligand concentration. This may happen if binding of toxin to its site at the receptor converts the site for the small ligand into one of much lower affinity. Much higher concentrations of small ligand would then be required for binding to this site. If occupied, however, a conformational change of the receptor is induced leading to accelerated dissociation of the bound toxin [74, 168, 169]. ▲: toxin, ◍: ligand. Dissociation rate constants for normal and accelerated dissociation: k_n and k_a, respectively.

tion (ca. 10 min). In the case of agonists, however, this is still too long to permit studies of the active form of the receptor. The desensitized form which dominates the equilibrium with agonists after the employed incubation times is characterized by relatively high binding affinities for agonists but only small positive cooperativity between the two agonist binding sites per receptor molecule (Fig. 10[303]). Special precautions and assay procedures are therefore required to reproducibly expose the weak positively cooperative interactions of the agonist binding sites at the receptor[303]. This is why the effect was observed in only some[299,300,303] but not all investigations[230,301,305]. In addition, the mathematical basis for the complete analysis of positively cooperative binding to two sites at a macromolecule has only recently been developed[81,82,303].

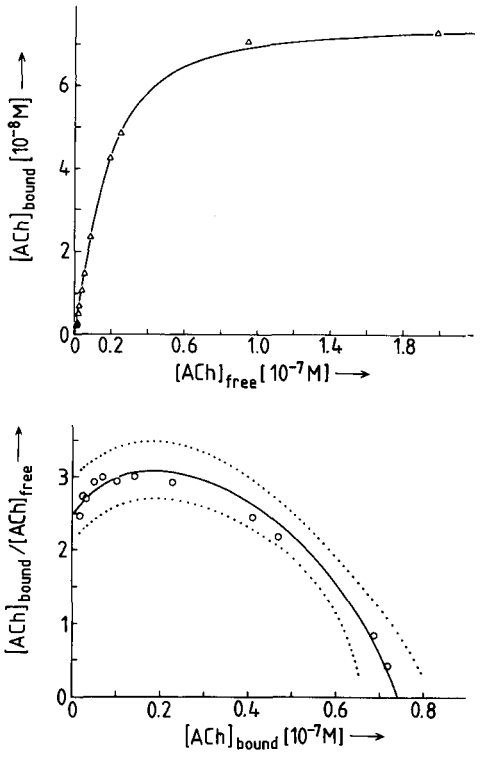


Fig. 10. Equilibrium binding of ^{3}H-acetylcholine to membrane fragments from *Torpedo mamorata* [303]. Binding equilibria were measured in 100 mM NaCl, 2 mM $CaCl_2$, 2 mM $MgCl_2$, 0.1 mg/mL bovine serum albumin, 0.25 mM tetram, 20 mM Tris/HCl, pH 7.2. Concentration of acetylcholine binding sites [Rec_0] = 37 nM. Above: Plot of bound versus free acetylcholine. Below: Scatchard plot of the binding data. 90% of all experimental points from a total of 56 independent binding experiments fall between the two dotted lines K_{D1} = 30 nM, K_{D2} = 6 nM. For data fitting see [303].

In summary, the binding studies with radioactively labeled cholinergic ligands of low molecular weight have produced only limited additional information but are much more difficult to carry out than binding studies with neurotoxins. Most noteworthy, they establish positively cooperative interactions of the binding sites for acetylcholine at the membrane-bound receptor in a non-physiological time-range[303]. This may support but certainly does not prove the earlier postulate[306] that strong positive cooperativity exists between the agonist binding sites of the active (non-desensitized) membrane-bound receptor.

6.1.3. *Irreversible Ligands*

The most thoroughly investigated chemical modification of the acetylcholine receptor is the reduction of a disulfide bridge in close proximity to the binding site for acetylcholine[82,85–95,299,307–311]. This reduction lowers the mean open time and the conductivity of the receptor channel[90,309–311] and the response to agonists with a single center of charge, but increases the response to agonists with more than one center of charge[85,86,307], reduces the Hill coefficients for agonists to 1[73,299], and converts hexamethonium to a cholinergic agonist[88]. With regard to the models of cholinergic excitation (Sections 3 and 7) it is noteworthy that irreversible linking of a single agonist per receptor molecule already suffices for channel activation[89,309,313]. After alkylation of the released SH groups with an affinity ligand—e.g. ^{3}H-bromoacetylcholine or ^{3}H-MBTA (see Section 4.3)—this label is found only in the α-subunit of the receptor. Depending on the reaction conditions and the receptor preparation employed, either only one[93,312] or both[94] of the released SH groups are labeled. While the disulfide reduction and alkylation experiments have identified the particular subunit of the receptor carrying the agonist binding site, no molecular basis exists as yet for the physiological effects of these modifications. This also applies to the discoveries that the irreversible reaction of BAC with single cell preparations of the electric eel leads to permanent depolarization of the membrane (no desensitization although the local concentration of BAC remains very high), and that the amide analogue of BAC, bromoacetylcholamine, under the same conditions also irreversibly binds to but does not activate the receptor[85,314]. These reactions if properly investigated and understood may offer crucial clues to the mechanisms of channel activation and desensitization.

The alkylating agent 3-bromomethyl-3′-trimethylammoniomethylazobenzene is of particular interest within the group of irreversible ligands because it can be photoisomerized from an inactive to a depolarizing ligand[315] and, thus, can be employed in concentration jump experiments. Most noteworthy of the results obtained with this ligand is that irreversible linking of a single molecule per receptor in its agonist conformation appears to suffice for channel activation[89,309,313], and that the rate of agonist binding to the receptor is not rate-determining for channel activation.

6.1.4. *Fluorescent Ligands of Low Molecular Weight*

Ligands with spectroscopic labels enable one to monitor their interaction with the receptor within the physiologically most important subsecond time range. While this is most important for kinetic studies (Section 6.2), these ligands are advantageous also for equilibrium binding experiments.

The chemical structure and spectroscopic and physiological properties of the existing fluorescent probes of the acetylcholine receptor have been discussed in detail[5]. Most suitable, and therefore most extensively used for biochemical studies have been derivatives of acetylcholine in

which the fluorescent moiety is separated from the cholinergic region by a bridge of methylene groups (Fig. 11). Of these, the unmodified NBD-n-acylcholines are pure agonists of acetylcholine[43,82,318–322], whereas the dansyl-n-acylcholines possess additional non-competitive properties[323,324]. Detailed binding studies have only been performed with the NBD-n-acylcholines. With the purified receptor from *Electrophorus* the binding of the fluorescent agonist is accompanied by complete quenching of the ligand's fluorescence[43,82,322]. The quenching is due to the formation of a hydrogen bond between the ω-amino group of the ligand as donor and an unknown acceptor group in a hydrophobic pocket of the receptor protein[322]. While the specificity of binding of the NBD-n-acylcholines is mediated by their cholinergic region[43,322], the changes in fluorescence clearly show that other regions of the fluorescent ligand also take part in the interaction with the receptor. This is why the binding affinity of NBD-n-acylcholines depends on the number of the methylene groups and why both binding affinity and fluorescence are affected by chemical modification of the ω-amino group[322].

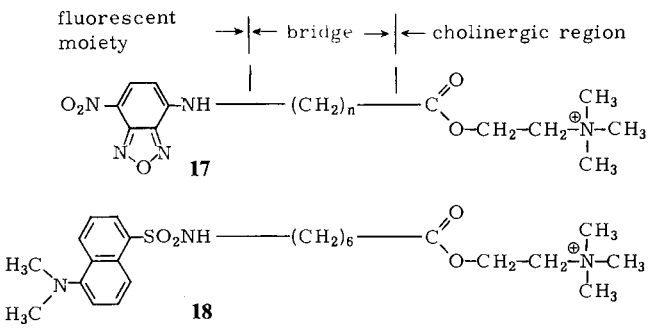


Fig. 11. Structural formulas of fluorescence-labeled acylcholines. **17**: "NBD-n-acylcholines" (systematic name: alkyl(dimethyl)-2-[ω-(7-nitro-4-benzofurazanylamino)-*n*-alkylcarbonyloxy]ethylammonium ion). **18**: "Dansyl-n-acylcholines" (systematic name: 2-[6-(5-dimethylamino-1-naphthalenesulfonamido)hexylcarbonyloxy]ethyl(trimethyl)ammonium ion or *O*-2-[6-(5-dimethylamino-1-naphthalenesulfonamido)hexylcarbonyl]choline. The n in the trivial name stands for the number of CH_2 groups.

The changes in ligand fluorescence caused by the interaction with the receptor permit direct and highly accurate measurements of the binding equilibria with the different receptor preparations[82]. Of particular importance in this context are the results of the competition binding studies with representative cholinergic ligands. They prove that cholinergic agonists and antagonists bind to the same number of binding sites at the purified receptor in a mutually exclusive fashion. The binding sites for antagonists form a single class of sites, those for agonists form two classes of sites with negatively cooperative interactions between each pair of sites. In agreement with electrophysiological observations under the same experimental conditions[85,88,90], incubation with dithiothreitol results in changes in affinity for some agonists; the binding patterns of a partial agonist and an antagonist under non-reducing conditions are changed to those of pure agonists[82].

The most important result of these studies is the proof of two different binding sites for agonists at the receptor. The equilibrium dissociation constants (Tables 2 and 3) obtained for antagonists are in agreement with the physiological data, those for agonists indicate partial or complete densititization of the receptor after the periods of incubation employed. Taken together, the experiments show that the receptor can be solubilized and purified without significant loss in function.

Studies with other fluorescent ligands[323–329] or marker molecules[330,331] were much less informative with regard to the mechanism of ligand interaction. With none of these, however, have more than one class of agonist binding sites or cooperative interactions of sites been observed. On the other hand, the studies of *Heidmann* and *Changeux*[324] and *Schimerlik* et al.[330] provide evidence of several affinity states of the receptor in the presence of agonists and for agonist-induced conformational changes.

6.1.5. Non-Competitive Blockers

Non-competitive blockers influence the response to cholinergic agonists by binding to separate sites at the receptor. While the maximal response to agonists is reduced in their presence, the apparent binding affinity for agonists is increased (smaller concentration required for half-maximal response). Typical members of this group of ligands are local anesthetics with amino groups such as procaine and dibucaine[287,300,338–340], hallucinogens such as phencyclidine[334,341], sedatives such as chloropromazine[335], various detergents[6], neurotoxins such as histrionicotoxin and anatoxin A[342–345], amantadine[346], the lipophilic methyltriphenylphosphonium ion[347] and a number of other natural and synthetic compounds of widely varying structure[348–352]. Electrophysiological studies with these compounds[35,332–334] lead to the suggestion that non-competitive blockers bind to parts of the ion-channel. It is equally probable, however, that they exert their effects through allosteric binding sites or through binding to the lipid phase[6,335–337].

In this context it is noteworthy, that non-competitive blockers do not bind to the purified receptor protein[82,168]. Consequently, only membrane-bound receptors can be used for in-vitro studies of these compounds. In this way, three types of binding sites for non-competitive blockers have been identified: One binding site per receptor molecule with high affinity (K_D in the micromolar range), a larger number of additional binding sites with at least an order of magnitude lower affinity which are probably located at the receptor-lipid boundary, and the binding sites for agonists to which a few of these compounds bind with even lower affinity (20—500 μM)[302,353]. Since all of these ligands possess more or less competitive properties[302,353,354] the name "non-competitive blocker" is confusing and is retained only for purely historical reasons.

All non-competitive blockers provide the membrane-bound receptor with increased affinity for agonists (Fig. 12[339,354]). Kinetic experiments indicate that this increase in affinity is due to conformational changes of the receptor

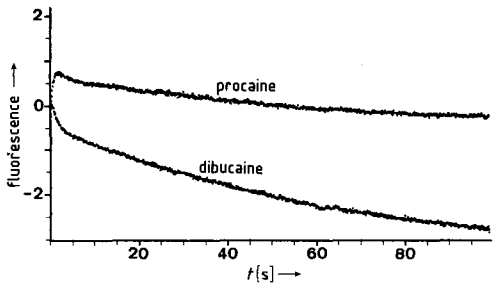


Fig. 12. Effect of non-competitive blockers on the interaction of NBD-5-acylcholine (Fig. 11) with the membrane-bound acetylcholine receptor from *Torpedo marmorata* [354]. The concentrations of membrane fragments [0.08 μM] and of fluorescent agonist employed [0.045 μM] corresponded to about 40% saturation of the available binding sites. Under these conditions, the addition of procaine (500 μM, upper oscilloscope trace) or dibucaine (10 μM, lower trace) induced a decrease in fluorescence, which is equivalent to additional binding of the fluorescent agonist. Binding of dibucaine exclusively causes an increase in the affinity for NBD-5-acylcholine (only a decrease in fluorescence is observed); in the case of procaine, the initial increase in and the equilibrium level of fluorescence both indicate that this local anesthetic can also compete with NBD-5-acylcholine for receptor binding. The rate constant for the decrease in fluorescence ($k = 0.01 \pm 0.005\ s^{-1}$) is reminescent of the slow process of desensitization observed in electrophysical experiments.

and that its time profile resembles that of the electrophysiologically defined phenomenon of desensitization[137,324,338,340,352,354]. Reconstitution experiments[355] suggest that at least some of the functional binding sites for non-competitive blockers are located at the receptor protein. Binding sites at the peripheral 43000-polypeptide[141,157] have been ruled out[137]. When affinity labeled with irreversible, radioactive non-competitive blockers, the label is found dominantly at the δ-subunit[356] but sometimes also at other subunits of the receptor[357].

The effects of non-competitive blockers are often taken as evidence in favor of the special allosteric model of the acetylcholine receptor[2,6,353]. In order to explain their mode of action, however, it already suffices to assume separate binding regions for each type of ligand (cholinergic agonist and non-competitive blocker) and interactions between these. Even the assumption of an allosteric model is not necessarily required, although this is tempting in view of the "modulating" effects of non-competitive blockers.

6.1.6. Antibodies

Antibodies against the acetylcholine receptor are useful tools, inter alia, for the following reasons: 1) Antibodies can be applied to studies of the structure of the receptor. 2) The acetylcholine receptor is a sufficiently simple preparation to quantitatively investigate the principles of antigen-antibody interactions and to analyze the effects of antibodies on the function of the receptor. 3) The molecular basis of the muscle desease *Myasthenia gravis* can be studied with the help of such antibodies. Here we shall concern ourselves mainly with the first aspect, and only just touch upon the others.

Modern approaches to the study of *Myasthenia gravis*[358-378] make use of the following two basic discoveries: The decreased number of functional acetylcholine receptors in the end plates of myasthenic patients[363] is evidence for a pathological change in the receptor concentration; the development of myasthenia-like symptoms after immunization of animals with foreign receptor protein[364] indicates an autoimmune component. In spite of the progress achieved in recent years[358-378], several alternative mechanisms for the induction and the various phases of this immune desease are still being discussed. Accordingly, *Myasthenia* is presently treated largely symptomatically[182,376-380].

Electrophysiological studies of myasthenic rats[370] show that their neurotransmission is reduced due to distinctly lower concentrations of functional receptor channels. In addition, an increase in the concentration of acetylcholine required to elicit half-maximal response (decrease in binding affinity) and changes in the kinetics of muscle excitation have been observed. The single channel properties of the remaining channels appear to be unchanged[370,376]. It has been difficult to show an immediate and direct blockade of receptor function by circulating antibodies[381,382].

Monoclonal antibodies (mAb) are particularly useful for structural studies of the acetylcholine receptor[383] because they are each directed against a single antigenic determinant at the receptor surface. Such determinants consist of only a few amino acids, so that the topography of the receptor can be studied with a high degree of resolution[123, 132, 159, 171-176, 182, 238-240, 369, 373, 380, 384, 385]. By means of the existing banks of monoclonal antibodies against the receptors of the electroplaques[175, 384, 385], at least 30 different surface determinants of the receptor can be distinguished. The most common applications of monoclonal antibodies have been the determination of subunit composition[130,158,386,387] and comparison of structures[175,374,388-390] of receptors from different sources. That much more penetrating investigations of receptor structure and function can be performed with monoclonal antibodies is exemplified in a structural analysis of the ligand binding regions of *Torpedo* receptor[175]. By employing an ELISA test (ELISA = *E*nzyme-*L*inked-*I*mmuno*s*orbent *A*ssay) in the selection of antibody-producing clones[174], monoclonal antibodies were also obtained against the binding regions for cholinergic ligands (agonists and antagonists)[175]. They differed from other antibodies against the receptor protein in that their binding to the receptor was completely blocked by α-cobratoxin. However, not all of these antibodies competed with low molecular weight ligands[175]: Three antibodies (mAbs 2—4) competed with all small ligands tested for binding to the receptor, a further two competed with all except the "bismethonium" compounds (mAbs 1,5), the sixth with all ligands except bismethonium compounds and tubocurarine. On the basis of the classical pharmacological occupational model (see Section 3[65], see also textbooks[391,392]) this implies that there are at least three types of binding sites for cholinergic agonists and antagonists at the receptor. Alternatively, it could be argued that the inability of some antibodies to bind to the receptor in the presence of certain ligands might be the consequence of a conformational change of the receptor induced by these ligands and leading to the disappearance of the appropriate antigenic determinant[175]. In other words, different ligands may cause different conformations of the

receptor; the receptor may not only distinguish between a few classes of ligands (agonist, antagonist, non-competitive blocker), and ligand recognition by the receptor may be of a much more individual nature.

Since all six antibodies competed with polypeptide neurotoxins for binding to the receptor[175], it was natural to assume that the binding sites for small ligands—even if they were different from each other—at least lie within narrow regions. By studying the competition of each pair of the six antibodies for receptor binding, it was shown that two such binding regions existed. Of particular analytical value in this connection was the fact that while antibody mAb 6 completely blocked the binding of the other five to the receptor, these could only partially block the binding of antibody 6. The simplest model accounting for these observations is shown in Figure 13. The essence of the initial data[175] has recently been confirmed by competition binding studies with radioactively labeled acetylcholine[393]. It was shown in this way that mAb 6 can only block half of the binding sites for acetylcholine.

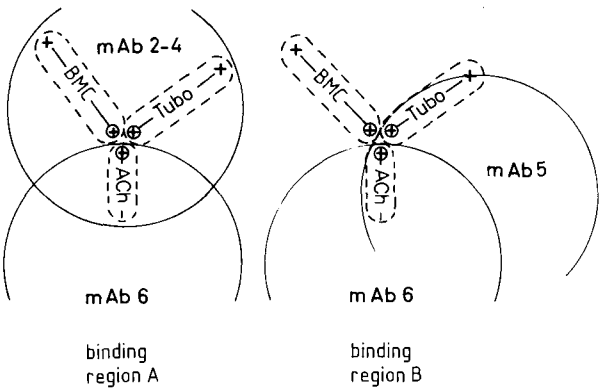


Fig. 13. A plausible model for the competition between monoclonal antibodies and cholinergic ligands [175]. The model assumes two binding regions—region A and region B—each consisting of three distinct ligand binding sites (subsites). Region A is defined by antibodies 2—4, region B by antibodies 1 and 5; the binding sites are defined by the ligands acetylcholine (ACh), tubocurarine (Tubo) and "bismethonium" compound (BMC) **8**, n = 6, 10. Antibody mAb 6 probably recognizes antigen determinants existing in both binding regions.

If such studies are extended to additional receptor functions (binding of non-competitive blockers and channel toxins, ion fluxes and conductivity changes), the surface areas of the receptor participating in these functions could be elucidated. This could lead to the structural localization of the ion channel and the areas involved in the coupling between the receptive and the responsive region(s).

The application of monoclonal antibodies in studies of receptor properties is only in its infancy. The preparation of these specific ligands is still a very new method[383] and basic questions such as the degrees of antibody specificity, the affinities, or the kinetics of interaction of monoclonal antibodies and antigens are still unclear or controversial. Also their basic advantage in comparison to immune sera, namely the reversibility of their action, has not yet been exploited to its full potential. New approaches to the analysis of receptor structure and function by immunological methods can also be expected from the recently available sequence data[197-201]. It now is possible to raise antibodies against synthetic peptides corresponding to particular segments of the receptor's sequence in order to test whether these segments are involved in particular functions of the receptor[197-201, 394, 395].

6.1.7. *Summary of the Equilibrium Binding Studies*

In summary, the equilibrium binding studies discussed here provide the following information on the organization and properties of the ligand binding sites at the receptor: The receptor monomer possesses two binding regions for competitive cholinergic ligands (agonists and antagonists). The two binding regions are structurally distinct[175]. This may explain why not only agonists[303] but also some α-neurotoxins[168] and one antagonist[301] have been found to bind to two classes of sites at the receptor.

In addition, there appear to exist in each of the two binding regions for competitive ligands different subsites for subclasses of these ligands[74, 175, 393]. Mutually exclusive binding of ligands with different subsites must then be due to structural alterations of the subsites for the other ligands after the first ligand is bound. Such model assumptions can also explain the ligand competition patterns of some monoclonal antibodies[175], the accelerated dissociation of receptor-toxin complexes in the presence of cholinergic ligands[74, 168, 169, 182], and other allosteric effects[283-285].

For non-competitive blockers there exist one specific binding site per ion-channel (receptor monomer) and additional binding sites at the boundary between receptor and the lipid environment and in the lipid phase. That the specific binding site for non-competitive blockers disappears with solubilization of the receptor may indicate that a specific protein-lipid-organization is required for the expression of this site. Since competitive and non-competitive ligands differ only in degree in their structure, every ligand of one group also has a certain affinity for the binding sites for the ligands of the other groups. This is more obvious for the non-competitive blockers because these are bound with comparatively low affinity and, therefore, are commonly employed in concentration ranges in which low affinity binding to other sites becomes significant.

The structure of the acetylcholine receptor is characterized by unusual flexibility and is easily influenced by bound ligands—including detergents[125, 168]. This variability in structure corresponds to the complexity of the electrophysiologically observed states of the receptor channel[44-49], and it therefore appears improbable that the functional properties of the receptor can be fully described by the assumption of only two or three states[2, 6, 72, 73]. Such models, therefore, should only be considered as working hypotheses in the phase of transition to a deeper understanding of this biological information transducing system.

The available equilibrium binding data cannot answer the question of how many agonist molecules must be bound to the receptor to activate the integral ion channel. However, under conditions of irreversible attachment of an agonist to the receptor, channel activation seems to require only a single molecule of agonist[309, 313, 316, 317].

6.2. Kinetic Studies

From the equilibrium binding data discussed in the preceding section the following conditions for kinetic studies of cholinergic excitation can be deduced: Since the active (ion conducting) state of the receptor is very short lived, biochemical studies of the molecular properties of this state require methods of similar or better time resolution. Such methods are fluorescent kinetic measurements of the binding reaction[43,324,328–331,396], ion flux measurements with high time resolution[243,344,9], and a combination of both[397]. In view of the complexity of the equilibrium binding studies with this receptor, it seems sensible to begin the kinetic studies with the simplest system available, i.e. purified receptor protein, and then to proceed from there to systems of higher complexity. As was shown by this approach[354,398], the membrane-bound receptor of receptor-rich membrane fragments possesses a much larger functional variability than does the purified receptor protein. This applies in particular to the interaction with non-competitive blockers and the mechanism of desensitization, making the membrane-bound receptor the preparation of choice for such studies[324,328–331,354]. Since ion flux measurements are measurements of the response, they have the same principle limits as have electrophysiological measurements. Since no direct data on the interaction between receptor and ligands can be obtained from such measurements, they will not be considered here in spite of their well developed techniques[9,389].

Of the existing techniques for fast kinetic studies of receptor-ligand interactions, the most suitable ones are those in which receptor and ligand for the first time meet during the actual experiment. This is particularly important for agonists and non-competitive blockers which modify the properties of the receptor within seconds[35,55,61,400]. Thus, methods in which an existing binding equilibrium between receptor and ligand is rapidly shifted[401] are not suited for studies of the active state of the receptor.

Crucial for the validity and significance of the results obtained are the properties of the monitoring effect and the pharmacological properties of the reactants. The monitoring effect should be specific and large in size, the pharmacology of the monitoring ligand should be clear-cut and as simple as possible. These conditions are best fulfilled by ligands—preferentially pure agonist or antagonist—the fluorescence properties of which change drastically and specifically upon binding to the receptor (for a detailed review of such ligands cf. [5]). Because of the considerable functional flexibility of the receptor, all other ligands or marker molecules[326–331] can easily lead to changes in the state of the receptor, thereby severely limiting the significance of such studies with respect to the physiological role of the receptor. As a consequence, we shall describe here mainly only experiments with the pure agonist NBD-5-acylcholine[10,43,318–322,354,396], and the partial agonists *N-n*-propyl-NBD-5-acylcholine[396] and dansyl-6-acylcholine[323–325,353,397] (see Fig. 11).

Binding of NBD-5-acylcholine to the purified receptor of the electric eel is accompanied by complete quenching of the ligand's fluorescence[43,82]. This large and specific effect was employed to study the kinetics of this interaction with the stopped-flow fluorimeter[396]. An initial analysis of the association kinetics showed that they are composed of several reaction steps and, therefore, cannot be analyzed in full detail without additional assumptions. To avoid these in the absence of an established mechanism, initially only the concentration-dependence of the initial rates of the association was analyzed. This yielded a second order forward rate constant of 2×10^8 M^{-1} s^{-1} for physiological buffer conditions at 20 °C and classifies the association reaction as very fast indeed[403] (Fig. 14).

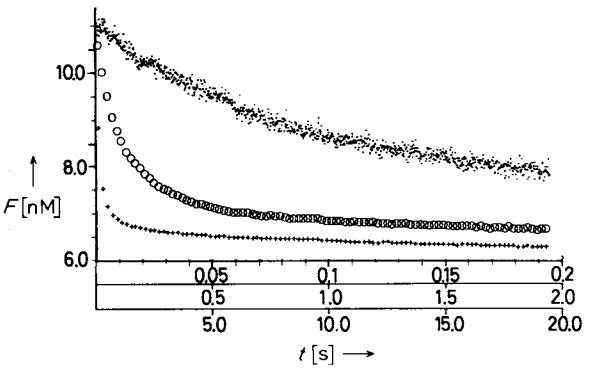


Fig. 14. Kinetics of association of NBD-5-acylcholine and the purified acetylcholine receptor from *Electrophorus electricus* [396]. Equal volumes of receptor (5.1 nM) and NBD-5-acylcholine (10.95 nM) were mixed rapidly in a stopped-flow-fluorimeter, and the decrease in fluorescence F was observed as a function of time t on a digital oscilloscope. Each of the traces shown is the average of four experiments. The three sets of experiments shown differ in their time ranges. These were 0.2—200 ms (•), 2—2000 ms (o), 20—20 000 ms (+). Of the set of experiments with the shortest time range, all 974 data points are shown, of the other two, every 10 points were averaged to one.

The dissociation kinetics were measured in two ways, each of them providing important information on the underlying molecular mechanism: When the kinetics of dissociation were measured after rapid dilution of the NBD-5-acylcholine-receptor complexes in excess of buffer, two kinetic components were observed under all experimental conditions. Since both components remain—even at low receptor saturation when only one of the two binding sites per receptor molecule is occupied—two forms of monoliganded receptor had to exist to account for two reaction steps (two kinetic components) in the dissociation kinetics. Thus, the following two alternative mechanisms could be written for dissociation of the half-saturated receptor [eqs. (d) and (e)].

$$[AR \rightleftharpoons AR^*] \rightleftharpoons R + A \qquad (d)$$

$$\begin{matrix} AR \\ RA \end{matrix} \rightleftharpoons R + A \qquad (e)$$

A = agonist, R = receptor,

(There exist two structurally different binding sites at the receptor; binding to and release from these sites are parallel processes.)

When the dissociation of NBD-5-acylcholine-receptor complexes was initiated by the addition of a large excess of a non-fluorescent competitive ligand, again at least two kinetic components were observed. While the initial rates of dissociation were independent of the type and concentration of the competing ligand and comparable with the first component of the dilution kinetics, the complexes dissociated all the slower in the later stages of the reaction, the higher the concentration of competing ligand (Fig. 15). In fact, the dissociation of complexes could be slowed down "beyond any limit" if only the concentration of competing ligand was increased accordingly (Fig. 15b). This property of the dissociation kinetics cannot be explained by a random mechanism of association and dissociation, not even when additional binding sites[74, 168, 283–285] or an allosteric mechanism[2, 6, 72, 73] are postulated. Under all these conditions the half-life of complexes should never increase beyond that defined by the most slowly dissociating component of the dilution kinetics (τ_2 in Fig. 15b), as is observed at sufficiently high concentrations of competing ligand. The observed dissociation kinetics, however, can be explained by the simplest strictly ordered mechanism [eq. (f)].

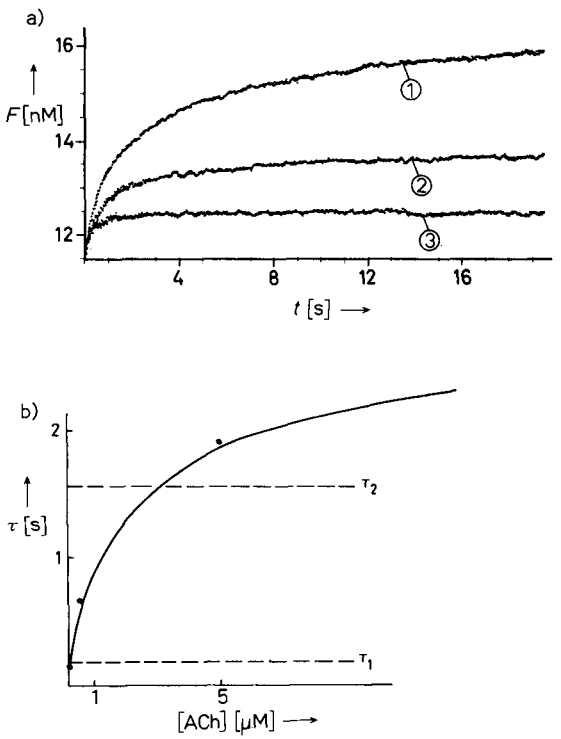
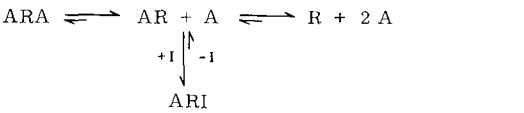


Fig. 15. Dissociation of NBD-5-acylcholine receptor complexes in the presence of a competing non-fluorescent ligand. a) Equal volumes of preformed complexes of NBD-5-acylcholine and the receptor, and of acetylcholine in standard buffer, were rapidly mixed and the increase in the fluorescence was recorded. Each trace shown is the average of four experiments carried out under identical conditions. Concentrations after mixing: receptor 5.05 nM; NBD-5-acylcholine 20.65 nM; acetylcholine 50 nM ③, 500 nM ② and 5000 nM ①. Time after which half of the NBD-5-acylcholine receptor complexes were dissociated: 96 ms in the absence of acetylcholine, 138 ms ③, 636 ms ② and 1900 ms ① in the presence of the concentrations of acetylcholine given above.—b) Half-lives τ of dissociation of NBD-5-acylcholine-receptor complexes plotted versus the concentration of acetylcholine employed. For comparison, the half-lives of dissociation by dilution (τ_1, τ_2) are included in the plot. As can be seen, the half-life of fluorescent complexes in the presence of competing ligands can exceed that of the slowest component of the dilution kinetics. This implies a strictly ordered mechanism, i.e. "first on—last off" of agonist dissociation from the receptor.

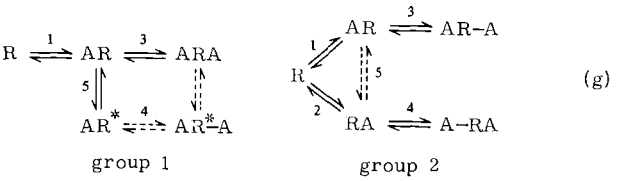


(f)

A = agonist, R = receptor, I = competing ligand

(To simplify the discussion we consider here only a single form of monoliganded receptor, cf. eqs. (d) and (e).) Under conditions of a strictly ordered mechanism, the dissociation of ARA (ARA→AR) (first component) would be independent of the presence of the competing ligand while the dissociation from AR (AR→R) would be hindered by the formation of ARI. The more ARI is formed, the less AR would be available for dissociation of the preformed complexes in the later stages of the reaction (Fig. 15). Hence, the dissociation of the fluorescent ligand-receptor complexes would be slowed down.

Taking together the results of both types of dissociation experiments, the following two groups of schemes are obtained for the interaction of the receptor with its ligands [eq. (g)].



(g)

(As shown by the broken lines, several variations of the basic schemes are possible. Plausible functional models for these reaction schemes are given in Figure 16.)

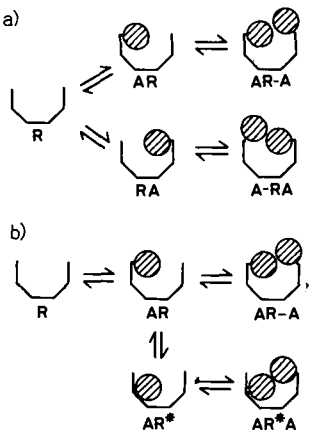


Fig. 16. Plausible models of the reaction schemes derived from fluorescence kinetics with NBD-5-acylcholine and the receptor protein from *Electrophorus* (Figs. 14 and 15). a) Two forms of the monoliganded receptor are formed in parallel from free receptor and free ligand. In the diliganded receptor, the ligand bound last sterically hinders the dissociation of the ligand bound first. Consequently, dissociation of ligands is strictly ordered and in the opposite order of succession as association.—b) Initially only one form of monoliganded receptor is formed (AR) but this form can spontaneously isomerize to a second form (AR*). The ordered dissociation of the diliganded receptor is caused by steric effects similar to those assumed in (a). The described effect of the ligand bound second must not be brought about by steric hindrance of the access to the binding site occupied first. The same effect could also result from allosteric interactions between the two binding sites.

Based on these schemes, simultaneous fits of combined sets of different association and dissociation kinetics and equilibrium binding experiments have been performed[396]. They provide the kinetic constants for all reaction steps considered in the reaction schemes. With these the competition kinetics with acetylcholine (Fig. 15) were fitted to obtain the kinetic constants for the interaction with the natural transmitter. The relevant data are given in Table 4.

Table 4. Reaction parameters for reaction scheme b) of Figure 16, obtained from simultaneous fits of equilibrium and kinetic studies with NBD-5-acylcholine and the purified acetylcholine receptor from *Electrophorus*.

Parameter	NBD-5-acylcholine [a]	Acetylcholine [b]
k_1 [M^{-1} s^{-1}]	4.8×10^8	5×10^8
k_{-1} [s^{-1}]	3.4	740
K_{D1} [M]	7.0×10^{-9}	1.5×10^{-6}
k_3 [M^{-1} s^{-1}]	3.4×10^8	5×10^6
k_{-3} [s^{-1}]	19.4	400
K_{D3} [M]	5.7×10^{-8}	8×10^{-5}
k_4 [M^{-1} s^{-1}]	7.9×10^6	1.5×10^5
k_{-4} [s^{-1}]	0.53	0.09
K_{D4} [M]	6.7×10^{-8}	6×10^{-7}
k_5 [s^{-1}]	0.52	170
k_{-5} [s^{-1}]	0.18	20
K_{D5} [M]	0.35	0.12
K_D (1) [M] [c]	1.8×10^{-9}	1.6×10^{-7}
K_D (2) [M] [c]	6.5×10^{-8}	6.7×10^{-7}

[a] The data for NBD-5-acylcholine were obtained from direct measurements. [b] The data for acetylcholine were obtained from displacement kinetics (cf. Fig. 15) keeping the parameter obtained for NBD-5-acylcholine constant. [c] K_D (1) and K_D (2) are the equilibrium dissociation constants relating to the two classes of sites observed in binding experiments [81]:

$$\frac{1}{K_D(1)} = \frac{1}{K_{D1}} + \frac{1}{K_{D1} \cdot K_{D5}}$$

$$\frac{1}{K_D(1) \cdot K_D(2)} = \frac{1}{K_{D1} \cdot K_{D3}} + \frac{1}{K_{D1} \cdot K_{D4} \cdot K_{D5}}$$

The data show that the two forms of saturated receptor, AR-A and AR*A, have very different properties. AR-A is formed quickly and dissociates quickly, AR*A is formed comparatively slowly and late but is much more stable. Because of its low K_D-value (acetylcholine), AR*A dominates at equilibrium. Since these properties of the two saturated forms of the receptor bear similarities to the active (ion conducting) and the desensitized (inactive) state of the receptor, the related reaction schemes have been proposed as "minimal models" for the mechanism of cholinergic excitation[396, 10]. When an event of cholinergic excitation is simulated on the basis of the kinetic data (Fig. 17), satisfactory agreement of the changes with time in the concentration of AR-A and the electrical events at the muscle end plates is found.

The kinetic study with NBD-5-acylcholine[396] led to the discovery of a strictly ordered mechanism of association and dissociation of agonists with the receptor. This has important consequences for the analysis of receptor kinetics and also for the mechanisms of ligand recognition and channel activation. Because the interaction between agonists and the receptor is ordered, the kinetics of interaction should not be analyzed by means of exponential fits[396, 404]

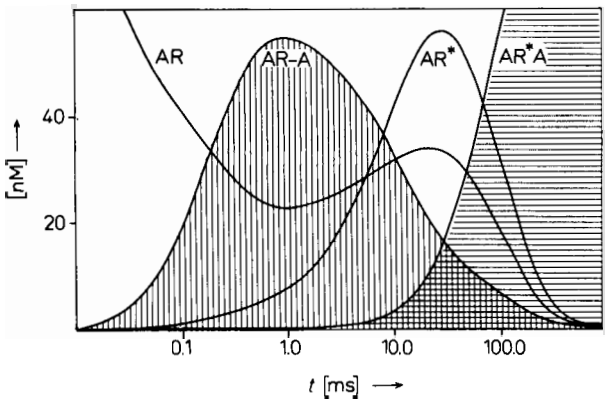


Fig. 17. Simulation of the transmitter binding reaction during an event of cholinergic excitation [396]. The data were calculated on the basis of the reaction scheme illustrated in Figure 16b with the minimal concentrations of acetylcholine receptor (1×10^{-7} M) and transmitter (1×10^{-4} M) present during the course of an excitatory event. The plot shows the intermediate nature of AR-A, its decay into AR* and later into AR*A. It has been postulated [10, 396] that AR-A represent the active state, AR*A are an inactive (desensitized) state of the receptor. In terms of the proposed correlation, the concentration versus time function for AR-A would then mimic the change in conductivity with time of a voltage-clamped muscle cell in the course of an event of cholinergic excitation. The decrease of AR-A with time would relate to the fast process of desensitization.

as was hitherto generally the case[9, 32, 243, 289–291, 323–331, 397, 398–401]. Under these conditions exponential fits not only result in incorrect kinetic constants but also in apparent additional kinetic components. This is why only a few of the previously obtained kinetic data, e.g. the rate constants of the first reaction step, can be compared with the data of ref. [396] without recalculation of the experiments. *Heidmann* and *Changeux*[324] have found a comparable rate constant of second order (9.5×10^7 M^{-1} s^{-1}) for dansyl-6-acylcholine and membrane vesicle from *Torpedo marmorata*. The comparatively low rate constants of other studies[401, 405] of around 1×10^7 M^{-1} s^{-1} are probably related to later reaction steps since they are based on effects which are *induced* but do not parallel the initial binding of acetylcholine to the receptor (corresponding to k_3 for acetylcholine in Table 4). *Heidmann* and *Changeux* have not described reaction steps with comparable kinetic constants. They did observe, however, another bimolecular *slow* reaction step ($k = 3.5 \times 10^5$ M^{-1} s^{-1}) for which there presently does not exist a simple correlation in the activation cycle of the receptor[255, 256, 406]. A further reaction step in the association kinetics of dansyl-6-acylcholine and *Torpedo* membrane vesicles ($k = 0.1$ s^{-1})[324] appears to be typical for the membrane-bound receptor and is also found using NBD-5-acylcholine (Fig. 12) as ligand[354, 398]. Other investigations[329, 331] have also identified similarly slow reaction steps for the interaction of the receptor with its ligands. On the basis of their time ranges, they probably relate to the transition from the active to the desensitized state of the receptor.

In summary, the kinetic studies described above already provide an independent contribution to the understanding of the dynamic properties of the acetylcholine receptor. The strictly ordered mechanism of association and dissociation of agonists probably could not have been found by

mere investigation of the response[7, 9, 24, 28, 35, 47, 49, 79b, 243, 244, 397]; but it has important implications for the mechanism of channel activation. The kinetic constants established from biochemical measurements set a frame for all physiological considerations concerning the relationship between channel activation and receptor saturation. For instance, the biochemical data disprove earlier ideas which saw desensitization as the result of a decrease in the affinity for agonists of the receptor. In contrast, the equilibrium binding and kinetic studies show that two forms of the agonist-saturated receptor exist, one of which being inactive (see Fig. 17). From a comparison of the electrophysiological and the biochemical data, however, it is clear that the latter are still too rough to provide a full molecular basis for all the functional states and substates of the receptor observed in physiological studies.

7. The Acetylcholine Receptor, Integral Signal Transducer of the Muscle End Plate

Rapid cholinergic transmission is a decisive factor for biological survival. Consequently, it must have been an early goal in the evolution of species to optimize the cholinergic synapse to high rates of signal reception, signal response coupling, and signal removal. This is achieved by the advantageous morphology of the synapse, an effective transmitter release system[27, 35, 64], and the combination of a rapid signal transducing (the receptor) with a rapid signal removing system (the esterase). Thus, as a result of the high concentration of acetylcholine esterase in the synaptic cleft[407, 408] and its extremely large turnover number[409] the concentration of acetylcholine fluctuates in the course of an event of cholinergic excitation from its basal to its maximal and back to its basal level within a few milliseconds. Cholinergic transmission is characterized, therefore, by very steep rises and descents of both the overall process and each single reaction step.

Within the reaction cycle of the transmitter[64], excitation of the receptor is only an intermediate side reaction (Figs. 1 and 18). The kinetic investigations with NBD-5-acylcholine (Fig. 11) and the purified receptor protein indicate that a similar mechanistic principle—the functionally significant reaction as an intermediate side reaction—also applies for the actual excitation process (Figs. 16—18). The active state of the receptor-ion channel attained by saturation with agonist is intermediate and short-lived, and rapidly reverts again to an inactive state. Under conditions of fully functional esterase and the usual concentration range of acetylcholine, this inactive state is the partially occupied or the free receptor; in the presence of constantly high concentrations of transmitter it is the desensitized state of the fully occupied receptor.

Since occupation of receptor by agonist is the triggering signal for channel activation, it is improbable that the active state of the receptor can also exist in the *absence* of agonist. Exactly this would be the consequence of the specific allosteric model (see also Section 3)[2, 4, 6, 8, 72, 73], which postulates that the different states of the receptor also exist in the absence of ligand, that they are in equilibrium with each other, and that merely this equilibrium is shifted by appropriate ligands. (According to this model, agonists have a higher affinity for the activated, antagonists a higher affinity for the inactive state of the receptor.) Single channel events, i.e. the activation of single receptor molecules, however, have never been observed in the absence of agonist. In addition, it has been unequivocally shown that a superstructure of the synapse[72] is not a necessary prerequisite for electrical excitation but that isolated receptors (extrasynaptic receptors) also are fully excitable. For these reasons, the specific allosteric model does not seem to be an appropriate basis for a molecular understanding of neuronal excitation processes, although evidence in favor of an equilibrium of states in the absence of agonists has frequently been reported to exist[2, 6, 8, 230, 233, 324, 328].

In contrast to the assumption of various states of the free receptor, it is clear, however, that the receptor saturated with agonist can exist in many states and substates[44–49, 175, 396]. Furthermore, there is strong evidence for allosteric interactions of rather distant regions of the receptor. In this connection it is noteworthy that non-competitive blockers exert their action preferentially on the receptor saturated with agonist. For these reasons it appears more appropriate to stress the plasticity of the *ligand-occupied* receptor in contrast to the free receptor. This is also in accordance with the general biological function of a signal transducer, i.e. to recognize ligands and to specifically re-

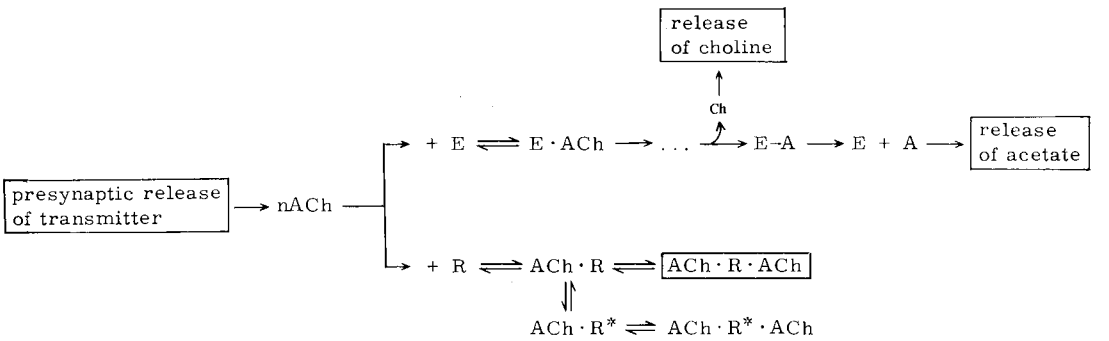


Fig. 18. Competition of acetylcholine receptor R and acetylcholine esterase E for the transmitter (see also Fig. 1b) [412]. From kinetic experiments with receptor and esterase and the fluorescent acetylcholine analogue NBD-5-acylcholine [321] (Fig. 11), the two macromolecules are found to have similar rate constants for initial binding of the transmitter. Consequently, receptor activation and enzymatic hydrolysis of transmitter are parallel reactions. Since receptor activation is a reversible process while transmitter hydrolysis is directed, the activation process can be considered an intermediate side reaction within the reaction cycle of the transmitter.

spond to their message. The fact that this apparently simple receptor system is capable of such a sensible recognition process indicates that it probably already possesses the essential molecular elements necessary for higher neuronal properties such as modulated response, selective information processing, and memory.

The significance of the established strictly ordered mechanism of ligand association and dissociation[396] must be seen in this connection. This mechanism is important, inter alia, for the following two central aspects of cholinergic transmission: 1) Binding of the first of the two agonist molecules per receptor can be fast because the monoliganded receptor is inactive under usual conditions. This is not to say, however, that this particular agonist-receptor complex is of little or no importance for activation. 2) In contrast, it is interesting that the stability of the initially formed agonist-receptor complex is strongly influenced by the occupation of the second binding site (ordered dissociation, "first on—last off"). Taken together, these effects may represent a key to the molecular mechanism of channel activation: Since *two* agonist molecules are required for channel activation, the specificity of excitation is increased; it is further enhanced by the ordered mechanism. In this way, an interaction characterized by low affinities and high forward and reverse reaction rates can obtain the specificity required for any signal receiving system. The periods of occupation of the first binding site may be even more important. To discuss this point, it is useful to depart from the models of rigid binding sites at the receptor and to consider instead models with "moving sites". In an ordered mechanism a shift of the initially bound ligand to a different position in the molecule is quite plausible and is indicated in the mechanism of acetylcholine hydrolysis by acetylcholine esterase[321,410]. If such a structural concept is assumed—binding of the agonist bound second "pushes" the agonist bound first to the activating position and keeps it there—both the usual pathway of receptor activation by two agonist molecules and the unusual activation by one irreversibly bound agonist molecule[89,309,313] can be explained: Activation may be induced by the ligand bound first, but only after this ligand has been shifted to and kept at the "activating position" for which binding of an additional agonist molecule is required. In the case of an agonist that can be linked irreversibly to the receptor, a second agonist molecule is only required for the attachment to the appropriate position but not any more for channel activation (it can be washed out). A plausible scheme demonstrating this mechanism in the context of the observed kinetics is shown in Figure 19. Continuing these arguments, desensitization would remain to be coupled to the periods of receptor occupation by agonist. If agonist remains available for longer periods of time than are defined by the stability of the active form of saturated receptor, the isomeric "desensitized" form of receptor develops. In the context of the above model, the agonist site occupied second (and/or additional "peripheral" sites) is likely to control desensitization: As was shown in experiments with single electroplaques of the electric eel, the irreversible attachment of one agonist per receptor molecule suffices to activate the receptor channel, but the end plate remains depolarized over long periods of time.

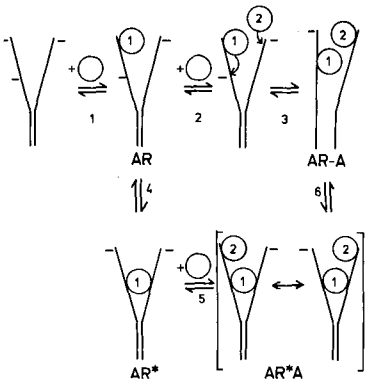


Fig. 19. A plausible model assuming "moving sites" for the agonist-induced activation of the acetylcholine receptor channel. It is proposed that binding of a second molecule of agonist to the receptor requires shifting of the agonist bound first from a peripheral to an inner binding site. This may occur rapidly (k_3, coupled with channel activation) or slowly (after previous isomerization of the receptor, k_4, and without effecting the state of the channel) (see also Figures 16—18). From the fluorescence kinetic studies with NBD-5-acylcholine and the receptor, AR-A is a metastable intermediate which is finally converted into AR*A.

The model conceptions described above are still new and require further testing. Consequently, they should rather be taken as an illustration for the present state of the studies on receptor mechanisms: Initially, the esterase was the subject of choice for the related studies[64], then the receptor was proposed as the central element of the excitation process[72,73], demonstrated and isolated[1,2,4], and subsequently identified as a transducer rather than a receptor of classical definition[12–14]. From the physiological and biochemical studies of recent years, the acetylcholine receptor has emerged as a rather complex system of ligand-modulated properties. With the exception of the resting state, all other states of the receptor appear to be induced and controlled by its ligands.

The structural and functional plasticity of the receptor should not divert from the fact that the basic reactions of receptor activation and inactivation follow well-defined molecular mechanisms. As one model for these mechanisms, ours[396] is based on exclusively biochemical data and does not contain any preconceived model assumptions. Its central element is the strictly ordered association and dissociation of the transmitter and its agonists to and from the receptor. As discussed here, this mechanism can provide molecular explanations not only for the basic electrophysiological observations, but, in addition, also for some experimental facts not understood by the previously available models. This model of cholinergic excitation may therefore be useful also for the investigation of other receptor systems including those of the central nervous system. This article may also illustrate the fact that a purely chemical approach to an understanding of receptor function does not suffice anymore at the present level of analysis, and that additional concepts and methods are required to unravel the molecular mechanisms by which biological cells communicate.

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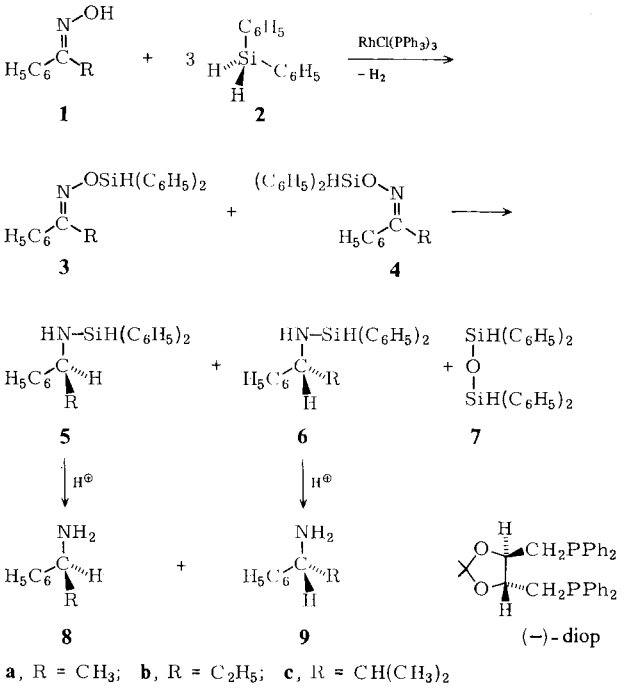
Enantioselective Catalytic Hydrosilylation of Oximes**

By *Henri Brunner** and *Richard Becker*

Whereas the hydrosilylation of alkenes, alkynes, and carbonyl compounds has been intensively investigated[1], only a few references appear in the literature on the corresponding reduction of compounds with CN double bonds[2]. Moreover, these only cover Schiff bases RR'C=NR'', R''≠H, whose hydrosilylation and hydrolysis lead to secondary amines RR'HC–NHR''. In the following, we report a novel method of hydrosilylating the CN double bond in oximes using diphenylsilane and rhodium-phosphane catalysts—a reaction which can also be controlled enantioselectively using optically active catalysts. By means of this novel reaction, oximes, and hence ultimately ketones, can be converted into optically active primary amines.

The reaction of 1 mol acetophenone oxime **1a** and 3 mol diphenylsilane **2** with ca. 1 mol-% $RhCl(PPh_3)_3$ in benzene was monitored by 250 MHz ^{1}H-NMR spectroscopy. After 10 min at −10 °C, the signals of **1a** disappeared. Apart from signals from small amounts of the final products **5a/6a** and **7**, initially only the signals of **3a** appeared [$\delta(CH_3)=2.1$ (s); $\delta(SiH)=6.03$ (s)]. The Rh-catalyzed silylation of **1a** to **3a**, which involves evolution of H_2, proceeds with retention of the *E*-configuration. In the course of the reaction the *E*-isomer **3a** is also converted into the *Z*-isomer **4a** [$\delta(CH_3)=2.2$ (s); $\delta(SiH)=6.05$ (s)]. Both isomers, **3a** more rapidly than **4a**, react to afford the final products **5a/6a** [$\delta(CH_3)=1.27$ (d), $J(CH_3CH)=6.7$ Hz); $\delta(SiH)=5.53$ (d), $J(SiHCH)=2.4$ Hz); $\delta(CH)=4.06$ (2q)] and **7** [$\delta(SiH)=5.85$ (s)]. After 24 h at room temperature only the signals of the final products **5a/6a** and **7** are present.

After addition of acetone and hydrolysis of the reaction mixtures with conc. HCl, 1-phenylethylamine **8a/9a** can be isolated in ca. 60% yield (Table 1) using catalysts generated in situ from $[Rh(cod)Cl]_2$[3] and (−)-diop[3]. The catalyst is still active even at Rh : **1a** ratios of 1 : 500. The best optical induction of 14.4% *ee* for (*R*)-**9a** is achieved with a twofold excess of (−)-diop at an Rh : **1a** ratio of 1 : 100. In order to determine the optical purity, a 1% solution of the trifluoroacetamide in ether, prepared from **8a/9a** using trifluoroacetic anhydride, is gas-chromatographed on a 25m



Chirasil-Val glass capillary[4], giving a base-line separation of the two enantiomers (column 105 °C, injector 230 °C).

Table 1. Hydrosilylation of **1a** (2.19 g), **1b** (2.37 g), or **1c** (2.64 g) with diphenylsilane **2** in 5 mL benzene.

Substrate	Rh : 1	Rh : P	1 : 2	*t* [h]	*T* [°C] [b]	Yield [%]	8/9 *ee* [%] [a]
Catalyst $RhCl(PPh_3)_3$							
1a	1 : 100	1 : 3	1 : 3	72	−10→25	30	—
1a	1 : 200	1 : 3	1 : 2,5	48	−10→25	30	—
Catalyst $[(cod)RhCl]_2$/(−)-diop							
1a	1 : 100	1 : 2	1 : 3	44	−10→25	54	4.5(*R*)
1a	1 : 100	1 : 2.4	1 : 3.2	24	−10→25	47	4.3(*R*)
1a	1 : 100	1 : 2.6	1 : 3.2	24	−10→25	56	5.2(*R*)
1a	1 : 100	1 : 2.8	1 : 3.2	24	−10→25	65	8.7(*R*)
1a	1 : 100	1 : 3	1 : 3.2	63	−10→25	59	10.0(*R*)
1a	1 : 100	1 : 3.2	1 : 3.2	24	−10→25	57	11.3(*R*)
1a	1 : 100	1 : 4	1 : 3.2	96	−10→25	60	14.4(*R*)
1a	1 : 200	1 : 4	1 : 3.2	96	−10→25	51	13.2(*R*)
1a	1 : 500	1 : 2	1 : 3	154	−10→25	60	5.3(*R*)
1b	1 : 200	1 : 3	1 : 3.2	192	25	29	5.8(*R*)
1b	1 : 200	1 : 3	1 : 3	24	50	39	7.6(*R*)
1c	1 : 200	1 : 2	1 : 3	144	25	20	18.9(*R*)
1c	1 : 200	1 : 2	1 : 3	44	50	30	12.7(*R*)

[a] Reproducibility ca. ±1%. [b] In reactions with **1a**, 1 h at −10 °C, followed by warming to room temperature.

Because of increasing steric hindrance, the analogous reactions with propiophenone oxime **1b** and isobutyrophenone oxime **1c** require either considerably longer reaction times at room temperature or the use of increased temperatures (Table 1).

Further studies should indicate how the novel method measures up against reduction with optically active $LiAlH_4$ reagents[5] and hydrogenation catalyzed by $H_4Ru_4(CO)_8(diop)_2$[6].

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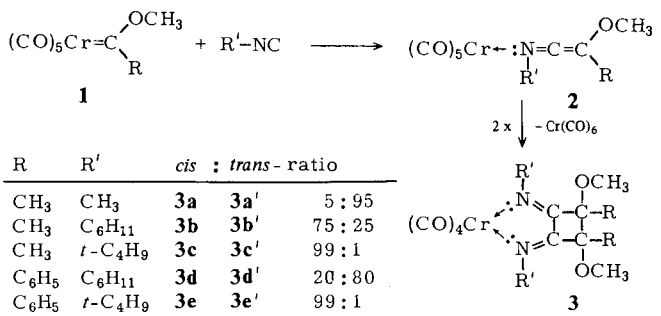
Metal Template for the Symmetrical [2+2]-Dimerization of Ketenimines**

By *Rudolf Aumann**, *Heinrich Heinen*, and *Carl Krüger*

Isocyanides insert smoothly into the M=C bond of transition-metal carbene complexes **1** of the Fischer-type to afford ketenimine complexes **2**[1-3], which react with a further equivalent of isocyanide[2] or with pyridine to release previously unknown ketenimines. The reactivity of the ketenimine ligands undergoes an umpolung in the complex: nucleophiles (e.g. CH_3OH) add to the terminal, but not—as in the free ketenimines—to the central carbon atom[2]. Nucleophilic attack results in simultaneous migration of the $Cr(CO)_5$ moiety from the nitrogen to the central carbon atom[1,2], producing aminocarbene complexes. Under certain conditions, aminocarbene complexes can also be obtained without addition of nucleophiles via (radical-induced) isomerization of the ketenimine complexes[1,2].

Thermolysis of **2** leads to novel, symmetrical [2+2]-dimerization of the ketenimine ligands to afford 1,2-bis(imino)cyclobutanes. Apparently this reaction involves participation of a metal template, since dimerization of free ketenimines leads to azetidines, diazetidines, or open-chain products[4]. Even when mildly heated, compounds **2** undergo dismutation to form $Cr(CO)_6$ and deep-blue $Cr(CO)_4$ complexes **3** which contain a 1,2-bis(imino)cyclobutane as chelate ligand. These complexes **3** occur respectively as *cis/trans*-isomer pairs (relative to the bond between the two sp^3 hybridized C atoms of the four-membered ring (cf. Fig. 1). The reaction becomes slower as the spatial demand of the substituent R′ increases and yields with increasing selectivity the *cis*-product.



R	R′	*cis*	: *trans*-ratio	
CH_3	CH_3	**3a**	**3a′**	5 : 95
CH_3	C_6H_{11}	**3b**	**3b′**	75 : 25
CH_3	t-C_4H_9	**3c**	**3c′**	99 : 1
C_6H_5	C_6H_{11}	**3d**	**3d′**	20 : 80
C_6H_5	t-C_4H_9	**3e**	**3e′**	99 : 1

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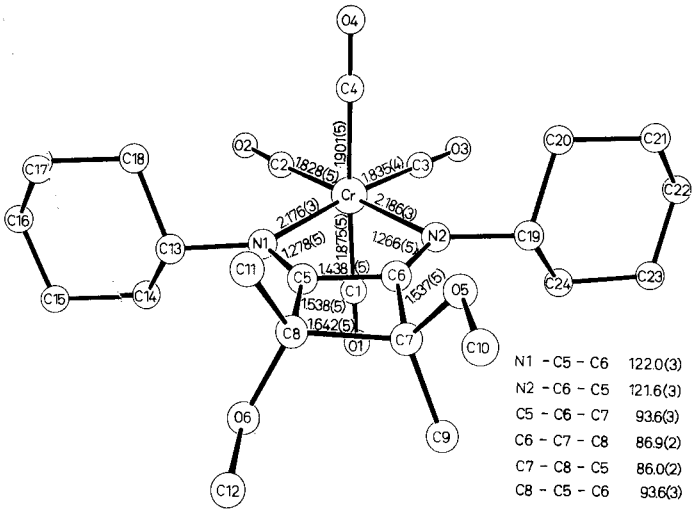
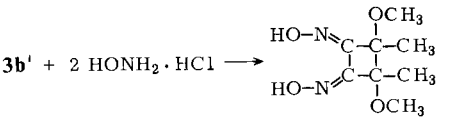


Fig. 1. Molecular structure of the chromium complex **3b′** in the crystal with selected distances [Å] and angles [°]. Crystal data: Space group $P2_1/c$ (No. 14), $a = 14.380(3)$, $b = 9.786(2)$, $c = 19.192(4)$ Å, $\beta = 102.65(2)°$, $V = 2635.20$ Å^3, $Z = 4$, $\rho_{calc} = 1.256$ g cm^{-3}; $\lambda = 0.71069$ Å, $\mu = 4.59$ cm^{-1}, $R = 0.051$, $R_w = 0.056$; 5958 measured reflections, 3283 of which observed ($I > 2\sigma(I)$); 298 refined parameters.—The existence of a high strain in the four-membered ring is expressed both by an extraordinarily long CC bond in the ring (C7–C8 1.642(5) Å) and by a deviation from the planarity of the system N1–C5–C6–N2: C7 −0.09 Å, C8 +0.11 Å. Axial and equatorial metal-carbon distances at the octahedrally coordinated Cr atom differ by 0.06 Å.—Further details on the crystal structure investigation can be obtained from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, by quoting the depository number CSD 50679, the names of the authors, and the journal citation.

The spectroscopic data of **3**[5] are consistent with those of other diazabutadiene complexes[6]. Compounds **3** are readily accessible via a one-pot reaction[7] and are relatively stable. They can be considered as depository compounds for 1,2-bis(imino)cyclobutanes and can be used as their synthetic equivalents: e.g., reaction of **3b** and **3b′** with two equivalents of hydroxylamine hydrochloride in methanol (50 °C, 0.5 h) yields the crystalline 1,2-bis(hydroxyimino)cyclobutanes **4b** and **4b′**[8].



4b (*cis*) + **4b′** (*trans*)

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[3] The yellow complexes **2** (R = CH_3, C_6H_5; R′ = CH_3, C_6H_{11}, t-C_4H_9) were recrystallized from hexane (−78 °C) and characterized by C,H,N analysis and by mass, IR, and ^{1}H-NMR spectroscopy.
[4] M. W. Barker, W. E. McHenry in S. Patai: *The Chemistry of Ketenes, Allenes and Related Compounds*, Wiley, New York 1980, part 2, p. 701–720.
[5] For example, values for **3b** and **3b′**: UV: **3b** λ_{max} in C_6H_{12} 660 nm ($\varepsilon = 6060$), in C_2H_5OH 610 (4900); **3b′** λ_{max} 680 (6850) and 630 (4500), respectively.—IR: ν(C≡O) for *cis*-$L_2Cr(CO)_4$ **3b** and **3b′** in hexane 2007 (40), 1903 sh (100), and 1845 (80); ν(C=N) 1590 cm^{-1}.—^{1}H-NMR (C_6D_6, 300 MHz): **3b′** $\delta = 3.02$ (OCH_3), 1.22 (CCH_3); **3b** $\delta = 3.15$ (OCH), 1.15 (CCH_3).—^{13}C-NMR (C_6D_6, 75 MHz): **3b′** $\delta = 15.26$ (CH_3), 25.10, 25.21 (2C), 34.36, 34.47 (5CH_2), 53.11 (OCH_3), 67.44 (NCH), 88.90 (*C*–OCH_3), 170.56 (C=N), 213.0 (*cis*-CO), 232.1 (*trans*-CO); **3b** $\delta = 18.66$ (CH_3), 25.06, 25.26 (2C), 34.11, 34.82 (5CH_2), 53.87 (OCH_3), 67.66 (NCH), 86.19

($C-OCH_3$), 171.16 (C=N), 212.43 and 213.01 (*cis*-CO), 232.29 (*trans*-CO).—FD-MS: **3b** *m/z* 498; **3b′** *m/z* 498.

[6] H. Bock, H. tom Dieck, *Angew. Chem. 78* (1966) 549; *Angew. Chem. Int. Ed. Engl. 5* (1966) 520; H. tom Dieck, I. W. Renk, *Chem. Ber. 104* (1971) 110; L. H. Staal, D. J. Stufkens, A. Oskam, *Inorg. Chim. Acta 1978,* 255; G. van Koten, K. Vrieze, *Adv. Organomet. Chem. 21* (1982) 151.

[7] Procedure for the synthesis of tetracarbonyl[1,2-bis(cyclohexylimino)-2,3-dimethyl-2,3-dimethoxycyclobutane]chromium(0) (**3b** and **3b′**): $(CO)_5CrC(OCH_3)CH_3$ [1] (250 mg, 1 mmol) is "dissolved" in 1 mL hexane in a 3 mL threaded flask (inert gas atmosphere and with exclusion of moisture), the mixture treated with a solution of cyclohexyl isocyanide (109 mg, 1 mmol) (FLUKA) in 1.5 mL hexane at −78°C and subsequently warmed to 50°C for 4 h. The deep-blue solution is rapidly chromatographed (since the complexes can decompose on the column) on silica gel (column 30 × 1.5 m, petroleum ether/ether = 4 : 1). The elution order is $Cr(CO)_6$, the ultramarine-blue **3b** (main product), and then the azure blue **3b′** (side-product). Total yields after recrystallizations from hexane (−78°C) ca. 200 mg (80%).

[8] **4b** and **4b′** give correct C,H,N values. **4b** (m.p. = 172°C) migrates more slowly than **4b′** (m.p. = 160°C) upon chromatography on silica gel. **4b′**: ^{1}H-NMR ($CDCl_3$, 300 MHz): $\delta = 1.60$ (CCH_3), 3.48 (OCH_3), 8.06 (br, OH); ^{13}C-NMR ([D$_6$]acetone, 75 MHz): $\delta = 13.52$ (CH_3), 54.56 (OCH_3), 78.13 ($C-OCH_3$), 155.56 (C=N); MS (70 eV): *m/z* 185 (6%, *M* − OH), 168 (8, *M* − 2OH), 153 (26, 168 − CH_3), 101 (100, 153 − NC−CN), 73 (56, 101 − CO).—**4b**: ^{1}H-NMR ($CDCl_3$, 300 MHz): $\delta = 1.60$ (CH_3), 3.56 (OCH_3), 8.06 (br, OH); ^{13}C-NMR ([D$_6$]acetone, 75 MHz): $\delta = 17.34$ (CH_3), 54.95 (OCH_3), 86.35 ($C-OCH_3$), 155.66 (C=N); MS (70 eV): **4b′**. The ^{13}C resonance signal of $C-CH_3$ in the *cis*-compound **4b** is observed at lower field than that of **4b′**. This effect was also invoked to explain the configurational arrangement in the complexes **3b** and **3b′**.

Dilithiomethylenecyclohexane—A Stable 1,1-Dilithioalkene**

By *Adalbert Maercker** and *Ralf Dujardin*

Among organopolylithium compounds, the 1,1-dilithioalkenes occupy the center of interest since, according to ab initio calculations on 1,1-dilithioethene[1], an orthogonal (perpendicular) double bond and, moreover, a triplet ground state should be preferred. Furthermore, an extremely low value was calculated for the barrier of rotation to a planar double bond[1]. The synthesis of a 1,1-dilithioalkane[2] suggested that the method used might also be applicable to the preparation of corresponding alkenes.

1,1-Dilithioethane has the disadvantage that, even at room temperature, it decomposes quantitatively in 8 h to afford vinyllithium and lithium hydride[2], a reaction which with 1,1-dilithioethene—assuming that it behaves analogously[1d]—would lead to the even more stable lithium acetylide. Our intention was therefore to synthesize a 1,1-dilithioalkene in which elimination of lithium hydride was precluded.

As starting material for the preparation of dilithiomethylenecyclohexane **4**, we used bis(chloromercurio)methylenecyclohexane **1**[3]. Treatment of **1** at room temperature with lithium powder (molar ratio ≈ 1 : 14) in diethyl ether under argon affords after 1 h a black suspension of **4**, LiCl, and lithium amalgam, which reacts with D_2O (gas chromatographically 81%, by distillation 51%) to form pure dideuteriomethylenecyclohexane **6**; the product is identical with that prepared using a Wittig reaction[4]. Under the conditions used for the deuteriolysis, **1** does not react with D_2O, even in the presence of lithium.

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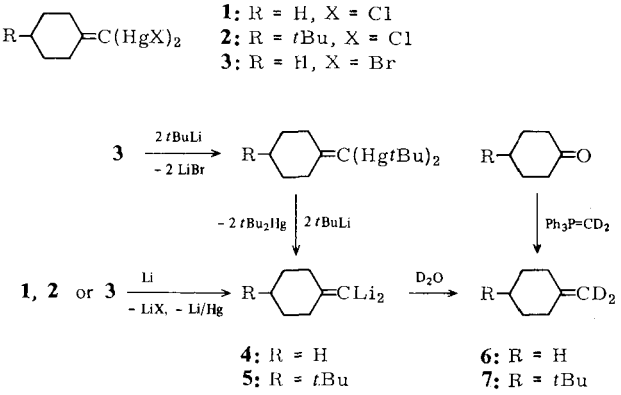
[**] Polylithium Organic Compounds, Part 2. This work was supported by the Fonds der Chemischen Industrie.—Part 1: [2].

An investigation of **4** by NMR spectroscopy has not yet proved possible since the compound is insoluble in ether and hydrocarbon solvents. The introduction of a *tert*-butyl group at the 4-position starting from 4-*tert*-butyl-1-bis(chloromercurio)methylenecyclohexane **2** also did not improve the solubility. **5** was also characterized by deuteriolysis, giving pure **7** (gas chromatographically 95%, by distillation 58%).



The dilithioalkene **4** can be obtained free of lithium amalgam and lithium halide if the bromomercury compound **3** is used and not allowed to react with lithium powder but with *tert*-butyllithium in cyclopentane[5]. This method has previously been used successfully to prepare 1,3-dilithiopropanes[6] and dilithiomethane[2]; however, it fails with the chloromercury compounds **1** and **2** as well as with 1,1-bis(chloromercurio)ethane[2].

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CAS Registry numbers:
1, 67091-33-2; **2**, 88766-94-3; **3**, 88766-95-4; **4**, 88766-96-5; **5**, 88766-97-6; **6**, 1560-57-2; **7**, 88766-98-7; bis(*tert*-butylmercurio)methylenecyclohecane 88766-99-8.

[1] a) Y. Apeloig, P. von R. Schleyer, J. S. Binkley, J. A. Pople, *J. Am. Chem. Soc. 98* (1976) 4332; b) S. Nagase, K. Morokuma, *ibid. 100* (1978) 1661; c) W. D. Laidig, H. F. Schaefer, III, *ibid. 101* (1979) 7184; d) Y. Apeloig, T. Clark, A. J. Kos, E. D. Jemmis, P. von R. Schleyer, *Isr. J. Chem. 20* (1980) 43.

[2] A. Maercker, M. Theis, A. J. Kos, P. von R. Schleyer, *Angew. Chem. 95* (1983) 755; *Angew. Chem. Int. Ed. Engl. 22* (1983) 733.

[3] A. Mendoza, D. S. Matteson, *J. Organomet. Chem. 152* (1978) 1.

[4] J. G. Atkinson, M. H. Fisher, D. Horley, A. T. Morse, R. S. Stuart, E. Synnes, *Can. J. Chem. 43* (1965) 1614.

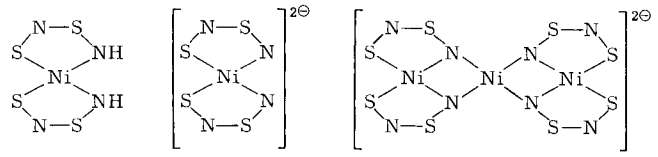
[5] *Procedure: tert*-Butyllithium (22 mmol), a large batch of which was previously prepared from di-*tert*-butylmercury and lithium (molar ratio 1 : 10) in cyclopentane, was added dropwise to an ice-cold solution of **3** (7.1 g, 11 mmol) in 30 mL anhydrous cyclopentane under argon. LiBr is filtered off from the clear solution using a filter frit under inert gas atmosphere; *tert*-butyllithium (22 mmol) is added again dropwise to the filtrate at room temperature. After being stirred for 2 h at room temperature, **4** is filtered off under an inert gas atmosphere and washed with anhydrous cyclopentane (5 × 50 mL) to remove di-*tert*-butylmercury and *tert*-butyllithium. For the deuteriolysis 10 mL D_2O is added dropwise at 0°C under argon, the mixture stirred for 10 min at room temperature, and ether added. The organic phase contains **6** (gas chromatographically 91%), which upon distillation affords 0.6 g (57%) pure **6**[4] of b.p. = 102−103°C. **6** was characterized not only by ^{13}C-NMR spectroscopy in $CDCl_3$ (=CD_2: $\delta = 105.8$, quint., $J = 25.4$ Hz) but also by GC/MS (glass capillary, silicon OV-101, length 30 m). The degree of deuteration of the exocyclic methylene group is 91% (MS).

[6] J. W. F. L. Seetz, G. Schat, O. S. Akkerman, F. Bickelhaupt, *J. Am. Chem. Soc. 104* (1982) 6848.

$[Ph_4P]_2[Ni_3N_8S_8]$, a Novel Trinuclear Complex with Sulfur-Nitrogen Ligands**

By *Johannes Weiss**

Alkalis react with the violet, planar complex $[Ni(HN_2S_2)_2]$ **1** to afford brown and red salts of the anions $[Ni(HN_2S_2)(N_2S_2)]^{\ominus}$ and $[Ni(N_2S_2)_2]^{2\ominus}$ **2**, respectively[1]. In turn, **2** can also act as a bidentate ligand in complexes. Thus with, e.g., $Ni^{2\oplus}$ the anion **3** is formed, a trinuclear complex in which two moieties of **2** are linked to each other via a further nickel atom.



1 **2** **3**

3 was isolated as the stable, black tetraphenylphosphonium salt $[Ph_4P]_2[Ni(NiN_4S_4)_2]$ **4**. This compound was initially formed unexpectedly when we attempted to convert the potassium salt of the anion of **2**[1], which only crystallizes with difficulty, into a more readily crystallizing salt with a larger cation by allowing it to react with Ph_4PBr. The initially formed $K[Ph_4P][Ni(N_2S_2)_2]$ recrystallizes from acetonitrile to afford **4**, which can also be obtained from **1** and $NiCl_2$ via directed synthesis[2]. Compound **4** is insoluble in cold water, is sparingly soluble in methanol or acetone, but is reasonably soluble in acetonitrile. Addition of acid to these solutions results in their immediate decomposition to re-form **1**.

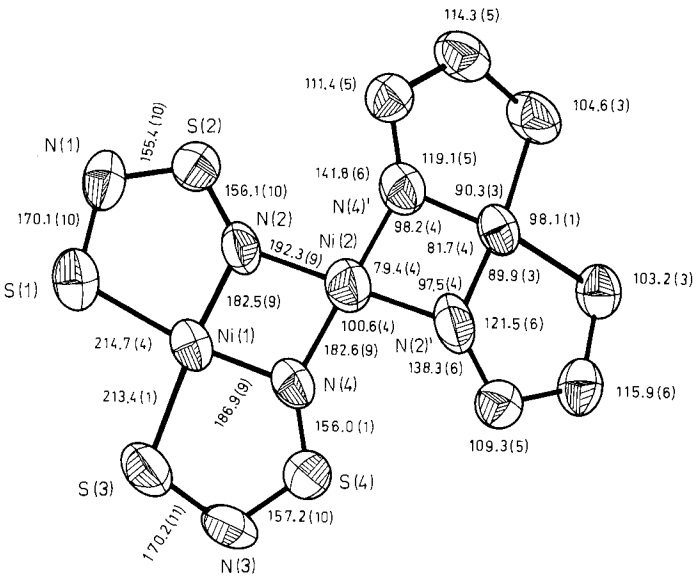


Fig. 1. Structure of the complex anion **3** in crystals of the tetraphenylphosphonium salt **4**. Bond lengths [pm] and bond angles [°], respectively, are shown in the left and right halves of the centrosymmetric anion. Space group $P2_1/a$, $a=1332.8(10)$, $b=1419.5(5)$, $c=1390.0(6)$ pm, $\beta=93.04(3)°$, $Z=2$; 2271 independent reflections with $I>2.5\sigma(I)$, $R=0.065$. Further details on the crystal structure investigation can be obtained from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen, by quoting the depository number CSD 50752, the names of the authors, and the journal citation.

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[**] Metal-Sulfur-Nitrogen Compounds, Part 15.—Part 14: H. Martan, J. Weiss, *Acta Crystallogr. C39* (1983) 959.

As indicated in Figure 1, the environment of the central atom Ni(2) in the centrosymmetric anion **3** and of the two peripheral Ni atoms is planar. The atoms of the individual "ligands" deviate only slightly from the best-fitting plane; however, these planes are each inclined by 17° to the coordination plane of Ni(2). The bond lengths and angles in the $[Ni(N_4S_4)]^{2\ominus}$ ligand scarcely differ from those in the complexed molecule **1**[3]. The only main difference is that the angle S(1)–Ni(1)–S(3) is ca. 8° larger and the angle N(2)–Ni(1)–N(4), ca. 11° smaller.

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CAS Registry numbers:
1, 50726-53-9; **4**, 88969-05-5; $K[Ph_4P][Ni(N_2S_2)_2]$, 89015-98-5.

[1] J. Weiss, *Z. Anorg. Allg. Chem. 502* (1983) 165.

[2] Procedure: **1** (1 g) and $NiCl_2 \cdot 6H_2O$ (0.5 g) are heated in 100 mL methanol until they dissolve, and a solution of Ph_4POH (2.9 g) in 50 mL methanol added dropwise. The mixture is stirred for 1 h without further heating. The green-black precipitate (2.1 g) is filtered off, dissolved in 200 mL acetonitrile, and heated to boiling; the solution is then filtered off, and after cooling, stored in the refrigerator. After a few hours, ca. 680 mg of small, dark colored, air-stable crystals form, m.p. = 245–247 °C.

[3] K. F. Mayer, J. Weiss, *Acta Crystallogr. B34* (1978) 1999.

1,2,3-Triaminocyclopentadienide Ions—Preparation via an Unusually Rapid Vinylcyclopropene-Cyclopentadiene Rearrangement**

By *Ekkehard Bartmann** and *Thomas Mengel*

Although cyclopentadienyl derivatives today form a vast class of compounds due to their importance as synthetic building blocks in the chemistry of natural products and as ligands in transition-metal complexes, only one general access to monoamino-substituted systems was previously known[1]. We describe here a facile synthetic pathway to 1,2,3-triamino-substituted cyclopentadienyl compounds, which, at the same time, is mechanistically interesting.

If the tris(dialkylamino)cyclopropenylium salts **1** (which according to *Yoshida* et al. are readily accessible[2]) are mixed with vinyllithium in the molar ratio 1:2 in tetrahydrofuran (THF) below −40 °C and the mixtures are carefully warmed, the salts dissolve with *simultaneous* evolution of ethylene. The reaction temperature is dependent on the steric demands of the cyclopropenylium ion and lies between ca. −10 °C (**1a**, **1c**) and +30 °C (**1b**). The solution contains the lithium salt of the respective 1,2,3-tris(dialkylamino)cyclopentadienide ion **2**, detectable in the NMR spectrum from the singlet exhibited by the ring protons at $\delta \approx 5.1$ as well as from its subsequent reactions.

The reaction can be explained as follows: Vinyllithium attacks **1** to form a vinylcyclopropenetriamine **4**; this immediately rearranges to the cyclopentadienetriamine **5**, which is deprotonated by additional organolithium reagents to afford **2**. The initial step (dissolution of the salt) is apparently the slowest, while the subsequent reaction pro-

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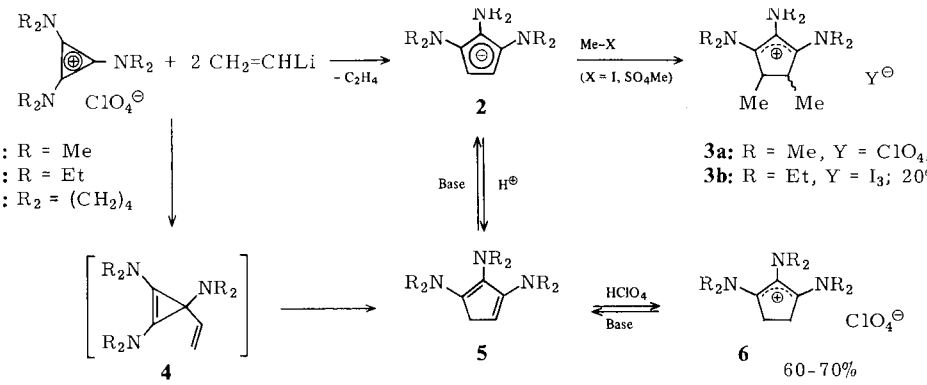
[**] Note added in proof: After completion of this manuscript, a synthesis of 1,2,4-triaminocyclopentadienyl cations was published: R. Gompper, H. Glöckner, *Angew. Chem. 96* (1984) 48; *Angew. Chem. Int. Ed. Engl. 23* (1984) 53.



ceeds extraordinarily smoothly for vinylcyclopropane-cyclopentene or vinylcyclopropene-cyclopentadiene rearrangements. Rearrangements of this type normally require considerably higher temperatures[3] (e.g. for triphenyl(vinyl)cyclopropene: 180°C) or irradiation[4]. The large number of amino substituents in **4** therefore effects a drastic reduction in the activation barrier (in general, highly donor-substituted cyclopropenes very readily undergo ring-opening reactions[5]. However, the rate of the vinylcyclopro*pane*-cyclopent*ene* rearrangement is also markedly increased by the presence of donor rather than alkyl substituents on the three-membered ring[3b,c]).

Upon acidification of the reaction solution, **2** is doubly protonated. The resulting cyclic 1,2,3-triamino-substituted vinamidinium salts **6** can be isolated as perchlorates[6]. The intermediate **5** has not yet been isolated, but its occurrence (possibly mixed with isomers) in solution is implicated: Addition of the weak proton donor *tert*-butyl alcohol to the solution of **2** results in the disappearance of its NMR signals and gives rise to a complicated spectrum; the characteristic signals of **6** appear only after addition of acids[8]. **2** can be re-formed from **6** by the addition of strong bases such as potassium hydride.

2 is also attacked twice by methylating agents to form 4,5-dimethyl-substituted salts **3**[6]. Whereas dimethyl sulfate reacts smoothly (isolation of the perchlorate **3a** starting from **1a**), in reactions with methyl iodide large amounts of by-products are formed (see also, the formation of the triiodide **3b** instead of the normal iodide)[9].

On the basis of preliminary results, the reaction of **1** with vinyllithium described here can be applied to its homologues (e.g. butenyllithium), but not to vinylmagnesium compounds.

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CAS Registry numbers:
1a, 36509-73-6; **1b**, 70674-11-2; **1c**, 61916-72-1; **2a**, 88968-35-8; **2b**, 88968-36-9; **2c**, 88968-37-0; **3a** (isomer 1), 88968-39-2; **3a** (isomer 2), 88968-41-6; **3b**, 88968-43-8; **6a**, 88968-45-0; **6b**, 88968-47-2; **6c**, 88968-49-4; CH_2=CHLi, 917-57-7.

[1] M. Bernheim, C. Boche, *Angew. Chem. 92* (1980) 1043; *Angew. Chem. Int. Ed. Engl. 19* (1980) 1010.
[2] Z. Yoshida, Y. Tawara, *J. Am. Chem. Soc. 93* (1971) 2573.
[3] a) Houben-Weyl-Müller: *Methoden der organischen Chemie, Band IV/3*, Thieme, Stuttgart 1971, p. 597–604, 714–716; b) H. G. Richey, D. W. Shull, *Tetrahedron Lett. 1976*, 575; c) B. M. Trost, P. H. Scudder, *J. Org. Chem. 46* (1981) 506, and literature cited therein.
[4] A. Padwa, *Acc. Chem. Res. 12* (1979) 310.
[5] a) M. T. Wu, D. Taub, A. A. Patchett, *Tetrahedron Lett. 1976*, 2405; b) R. Gompper, K. Schönafinger, *Chem. Ber. 112* (1979) 1514; c) R. Weiss, H. Wolf, *ibid. 113* (1980) 1746; d) H. Yoshida, M. Nakajima, T. Ogata, K. Matsumoto, R. M. Acheson, J. D. Wallis, *Chem. Lett. 1983*, 155, and literature therein.
[6] *Procedure:* **3** and **6**: A solution of vinyllithium[7] (0.7 g, 20.5 mmol) in 10 mL THF was added dropwise to a suspension of **1** (10 mmol) in 10 mL THF at −78°C and the solution then slowly warmed until reaction commenced. When evolution of gas had ceased, the mixture was maintained at 30–40°C for 1 h, and the electrophile (conc. perchloric acid, methyl iodide, or dimethyl sulfate) added in excess (30–40 mmol) at −78°C. After warming to RT (and for the methylation after additional stirring for 24 h at RT), the mixture is concentrated to ca. 5 mL in vacuo, the residue treated with 20 mL water, and the aqueous phase extracted with dichloromethane (3 × 10 mL). The extracts were loaded onto a silica gel column, and the product fraction eluted with acetone (**3a**, **6a**, **6c**) or THF (**3b**, **6b**). The eluate was concentrated in vacuo and the residue recrystallized from chloroform/ethyl acetate: colorless or violet-brown (**3b**) crystals; **3a**: m.p. = 112–117, **3b**: 124, **6a**: 131, **6b**: 96–97, **6c**: 161°C; yields, see Scheme 1. All compounds gave correct C,H,N-analysis values.
[7] B. Bogdanovic, B. Wermeckes, *Angew. Chem. 93* (1981) 691; *Angew. Chem. Int. Ed. Engl. 20* (1981) 684.
[8] ^{1}H-NMR ($CDCl_3$): **6a** (R = Me): δ = 2.54 (s, 6H), 2.75 (s, 4H), 3.29 (s, 12H); **6b** (R = Et): 1.01 (t, 6H), 1.28 (t, 12H), 2.83 (q, 4H), 2.90 (s, 4H), 3.66 (q, 8H); **6c** (R_2 = $(CH_2)_4$): 1.75–2.25 (m, 12H), 2.82 (s, 4H), 2.99 (mc, 4H), 3.65 (mc, 8H).
[9] **3a** crystallizes as a mixture of *cis*- and *trans*-isomers; **3b** appears to consist largely of the pure *trans*-isomer. ^{1}H-NMR ($CDCl_3$): **3a**: δ = 1.24/1.28 (2d, together 6H), 2.54/2.55 (2s, together 6H), 2.65 (mc, 2H), 3.30/3.33 (2s, together 12H); **3b**: 1.05 (t, 6H), 1.34 (d, 6H), 1.36 (t, 12H), 2.78 (q, 2H), 2.90 (mc, 4H), 3.77 (mc, 8H).

Non-Toxic Alternative for a Key Step in Porphyrin Synthesis**

By *Theo Wollmann* and *Burchard Franck**

The oxidative rearrangement of acetylpyrroles such as **1** to pyrrolacetic acids **4** is a key step in the synthesis of porphyrins with "natural" acetic acid side-chains. Until now this rearrangement, whose result is analogous to the Willgerodt reaction, was performed using thallium(III) nitrate[1]. The toxity of this reagent, however, restricts the usefulness of the method and also the application of the synthesized products for medicinal purposes. Here, we describe an efficient, generally applicable method for the rearrangement of acetylpyrroles in the presence of silver nitrate (Scheme 1).

The pyrroleacetic acids **4a** and **4b** are of preparative importance because they permit the biomimetic syntheses of medicinally used porphyrins in a few steps[2]. For example,

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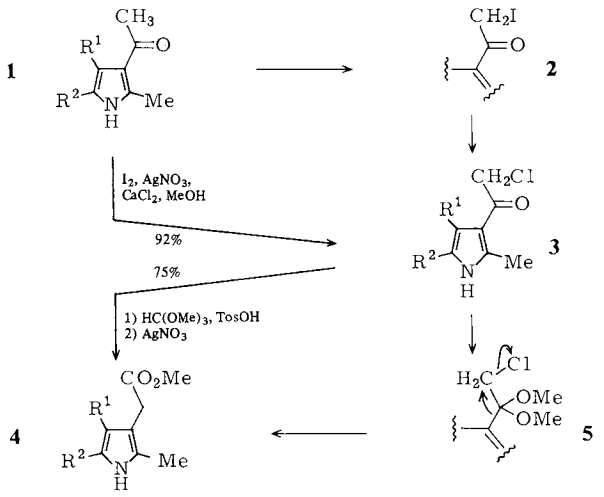
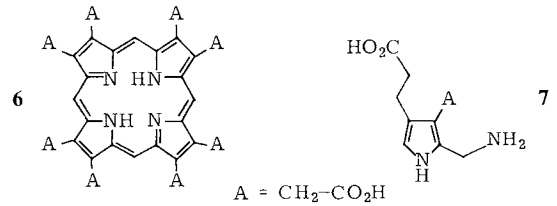


a, $R^1 = CH_2{-}CO_2Me$; $R^2 = CO_2Me$
b, $R^1 = CH_2{-}CH_2{-}CO_2Me$; $R^2 = CO_2CH_2Ph$

Scheme 1. Intermediates and possible course of the reaction **1**→**2**→**3**→**5**→**4**.

4a can be converted in three steps into the porphyrinoctaacetic acid **6**, which differs only slightly from the biologically active naturally occurring porphyrins[3]. **4b** can be converted in five steps into the porphobilinogen **7**, a building block in the biosynthesis of red blood pigment[4]; **7** can be condensed biomimetically to afford porphyrins.



Investigations of the mechanism of the oxidative rearrangement of simple aryl ketones indicated that the system thallium(III) nitrate in $MeOH/HClO_4$ can be replaced by $I_2/AgNO_3$[5]. The reaction sequence involves α-halogenation of the ketone, ketalization, and rearrangement of the α-haloketal to the acetate induced by silver ions (**1**→**2**→**5**→**4**).

By fulfilling certain restrictive reaction conditions, we found that using this method the acetylpyrrole **1b** can be converted into the triester **4b**. Because of the formation of side products, which necessitate chromatographic separation the method is still too troublesome for preparative purposes. Furthermore, studies indicated that side products arise because of the instability of the intermediate iodoacetylpyrroles **2**. These problems could be solved by trapping **2** by conversion into the chloroacetylpyrroles **3**. The chloroacetylpyrroles **3a** and **3b**, obtained in high yield, are readily isolable and form good crystals[6].

For the rearrangement, **3a** and **3b** are converted into the ketals **5a** and **5b**, respectively, which are refluxed in the presence of silver nitrate. The yield of the rearrangement step to afford **4a** and **4b**, respectively, is so high that the overall yield starting from **1a** or **1b** is 68–69%. The yields obtained using the new method correspond to those achieved in the rearrangement with thallium(III) nitrate, but the former is preferable because of its non-toxicity. The silver can be fully recovered from the silver halide precipitates.

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CAS Registry numbers:
1a, 73869-95-1; **1b**, 62916-29-4; **3a**, 88915-86-0; **3b**, 88915-87-1; **4a**, 73869-96-2; **4b**, 50622-64-5; $(MeO)_3CH$, 149-73-5; I_2, 7553-56-2; $AgNO_3$, 7761-88-8.

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[5] S. D. Higgins, C. B. Thomas, *J. Chem. Soc. Perkin Trans. 1 1982*, 235; C. Giordani, G. Castaldi, F. Casagrande, A. Belli, *ibid. 1982*, 2575.

[6] *Preparation of chloroacetylpyrroles* **3**: $AgNO_3$ (17 g, 100 mmol) and **1** (50 mmol) are added to anhydrous $CaCl_2$ (25 g, 225 mmol) in 150 mL anhydrous methanol. A solution of iodine (12.7 g, 50 mmol) in 100 mL anhydrous MeOH is added dropwise into the refluxing solution over 2 h, the mixture heated for 1 h longer, the solution filtered while hot, and the precipitate washed with hot MeOH. After the filtrate has been diluted with a threefold volume of water, the solution is saturated with NaCl, extracted with $CHCl_3$, the extract concentrated, and the residue recrystallized from $MeOH/H_2O$. 91% **3a**, colorless needles, m.p. = 149–150°C; **3b**, colorless needles, m.p. = 109–110°C.

[7] *Rearrangement of* **3** *into the pyrroleacetic acids* **4**: *p*-Toluenesulfonic acid (200 mg) was added to a solution of **3** (45 mmol) in 175 mL anhydrous MeOH and 50 mL (460 mmol) trimethylorthoformate, the mixture warmed to 50°C, and stirred for 1–2 h under an inert gas atmosphere. After conversion of the starting material into the ketal **5** (TLC monitoring with ether (**3a**) or toluene/acetic acid = 4:1 (**3b**) on silica gel), $AgNO_3$ (11.8 g, 67.5 mmol) is added. The mixture is refluxed for 5–7 h until **5** has been fully converted into **4** (TLC monitoring). After addition of KI (4 g) and cooling, the solution is filtered off, the filtrate diluted with a threefold volume of water, saturated with NaCl, extracted with $CHCl_3$, concentrated, and the oily residue recrystallized from ether/petroleum ether (b.p. 30–60°C). 75% **4a**, m.p. = 92°C; 76% **4b**, m.p. = 78°C.

3-Trimethylsilylacrylic Acid as an Acetylene Equivalent in Diels-Alder Reactions; Olefins via Anodic Decarboxylation-Desilylation**

By *Dieter Hermeling* and *Hans J. Schäfer**

Synthetic equivalents for acetylene which have a greater dienophilicity and lower pressure sensitivity are desirable for the preparation of 1,4-cyclohexadienes by [4+2]-cycloaddition. In this connection, (*E*)-1-benzenesulfonyl-2-trimethylsilylethylene[1] and maleic acid anhydride have proved to be particularly useful. The maleic acid cycloadducts undergo facile anodic bisdecarboxylation to afford olefins[2]. However, low yields and electrode passivation frequently limit the range of application and the scale of the electrolysis. We have now investigated 3-trimethylsilylacrylic acid **1** as an acetylene equivalent. The trimethylsilyl moiety lowers the dienophilicity only marginally[1], and the β-trimethylsilylcarboxylic acid obtained can be converted anodically into an olefin[3].

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[**] Anodic Oxidation, Part 31. This work was supported by the Fonds der Chemischen Industrie.—Part 30: G. Schlegel, H. J. Schäfer, *Chem. Ber.*, in press.

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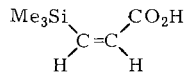
1 was prepared by Lindlar hydrogenation of 3-trimethylsilylpropiolic acid **2** (88% yield), obtained by silylation of propargyl alcohol and subsequent chromic acid oxidation. **1** adds smoothly to cyclopentadiene and isoprene (Table 1); for **2** higher temperatures are required, and these conditions lead to partial desilylation. The most reactive compound is the acid chloride **3**, obtained from propargyl alcohol by silylation, $LiAlH_4$ reduction, CrO_3 oxidation, and treatment of the product with $SOCl_2$.



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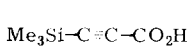

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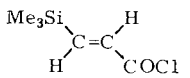

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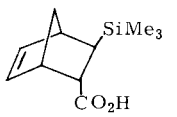

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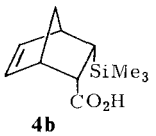

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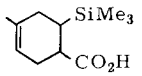

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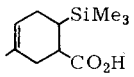

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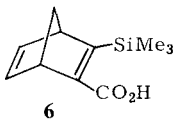

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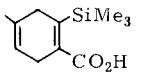

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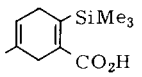

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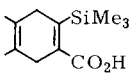

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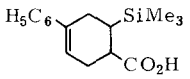

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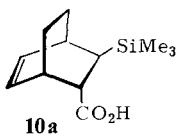

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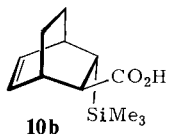

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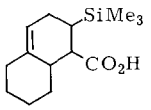

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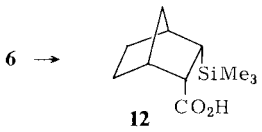
Table 1. Diels-Alder reactions [a] with **1**, **2**, and **3**.

Diene [b]	Dienophile	T [°C]	t [h]	Adducts [c]	Yield [%]
cyclopentadiene (10)	**1**	20	24	**4a**, **b** (5:2)	78
isoprene(10)	**1**	90	24	**5a**, **b** (1:1)	73
cyclopentadiene(10)	**2**	60	12	**6**	75
isoprene(10)	**2**	120	18	**7a**, **b** (1:1)	66
2,3-dimethylbutadiene(10)	**2**	120	18	**8**	70
2-phenyl-1,3-butadiene(3)	**3**	20	24	**9** [d]	89
1,3-cyclohexadiene(1.5)	**3**	60	24	**10a**, **b** (8:2) [d]	80
1-vinyl-1-cyclohexene(2.5)	**3**	60	18	**11** [d]	83

[a] General procedure: Diene and dienophile were allowed to react neat. Adducts **4**, **5**, **7**, and **8** were extracted with 2N NaOH after acidic impurities had been removed with $NaHCO_3$ (Na_2CO_3 for **7** and **8**). **9**–**11** cannot be extracted with NaOH and after hydrolysis were purified by column filtration (CH_2Cl_2/EtOAc 5:1 to 25:1). Purification of **6**: Extraction with Na_2CO_3, recrystallization from MeOH/H_2O. [b] Data in parenthesis: mol diene per mol dienophile. [c] Data in parenthesis: isomer ratio. [d] After hydrolysis.

Since α,β-unsaturated carboxylic acids cannot be decarboxylated anodically, **6**–**8** were hydrogenated (Pd/C, methanol). **6** afforded **12** quantitatively, whereas **7** gave the three isomeric carboxylic acids **13** in 86% yield together with 9% *p*- and *m*-methylbenzoic acids. With **8** aromatization was even more dominant: In addition to 51% 3,4-dimethylbenzoic acid only 42% of the five diastereomeric acids **14** were formed.—Hydrogenation of **9** yielded **15**.



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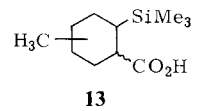

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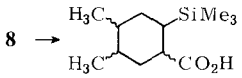

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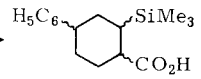


15

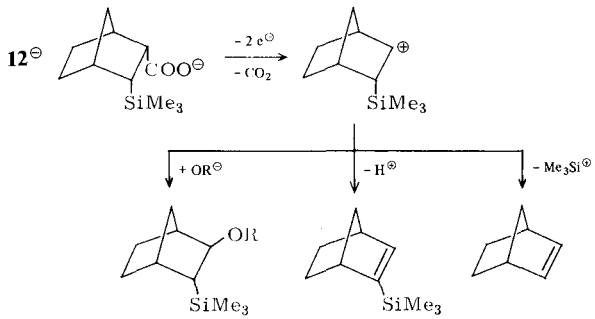
To establish the optimum conditions for formation of olefins, the potassium salt of **12** was electrolyzed under various conditions (Table 2). Formation of the products **16**–**18** indicates the involvement of an intermediate trimethylsilylnorbornyl cation which undergoes solvolysis, deprotonation, and desilylation.

Table 2. Electrolysis [a] of the potassium salt of **12** under various conditions.

Solvent	T [°C]	Cell potential [V]	Product yields [%] [b] **16a**	**16b**	**17**	**18**
pyridine/methanol (5:1)	20	80–150	10	—	45	26
methanol	0	60–80	44	—	13	19
acetonitrile/methanol (5:1)	0	8–20	31	—	7	35
acetonitrile/ethanol (5:1)	0	8–20	—	17	14	51
acetonitrile/ethanol (5:1)	60	8–20	—	9	13	60

[a] 0.2 mmol acid in 20 mL solvent and 4 mL 0.05N KOH in ethanol or methanol were electrolyzed using a graphite anode (8 cm^2) and a platinum foil cathode. Current density 10–20 mA/cm^2. [b] Determined by gas chromatography (capillary column SE-30).

The remaining β-trimethylsilylcarboxylic acids were allowed to react in the most favorable electrolyte (acetonitrile/ethanol (5:1)) (Table 3). In general, the yields were better than with **12**; in contrast to **12**, increasing the temperature caused no increase in yield. With **5** the current consumed should not substantially exceed 2 F/mol since otherwise the product is oxidized to toluene. The other olefins are stable under the electrolysis conditions.



16a: R = CH_3
16b: R = C_2H_5

17 **18**

We believe that the anodic decarboxylation-desilylation is an attractive alternative to anodic bisdecarboxylation. The reaction does not result in electrode passivation and gives good yields. This becomes particularly noticeable

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Table 3. Anodic oxidation of β-trimethylsilylcarboxylic acids in acetonitrile/ethanol (5 : 1) [a].

Acid	T [°C]	Product	Yield [b] [%]
4a, b	20	2,5-norbornadiene	76
5a, b	20	1-methyl-1,4-cyclohexadiene [c]	67
11	20	bicyclo[4.4.0]deca-1,4-diene	83 [d]
12	60	2-norbornene	60
13	20	4-methyl-1-cyclohexene	73
14	20	4,5-dimethyl-1-cyclohexene	89
15	20	4-phenyl-1-cyclohexene	91 [d]

[a] See Table 2 for electrolysis conditions. [b] Determined by gas chromatography. [c] Including 10% toluene. [d] Isolated yield.

when the 15% yield of 2,5-norbornadiene from 5-norbornene-2,3-dicarboxylic acid[2b] is compared with the 76% obtained starting from **4**.

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CAS Registry numbers:
1, 88946-47-8; **2**, 5683-31-8; **3**, 88946-48-9; **4a**, 88946-49-0; **4b**, 88946-50-3; **5a**, 88946-51-4; **5b**, 88946-52-5; **6**, 88946-53-6; **7a**, 88946-54-7; **7b**, 88946-55-8; **8**, 88946-56-9; **9**, 88946-57-0; **10a**, 88946-58-1; **10b**, 89015-36-1; **11**, 88946-59-2; **12** (isomer 1), 88946-66-1; **12** (isomer 2), 88946-65-0; **13**, 88946-60-5; **14**, 88946-61-6; **15**, 88946-62-7; **16a**, 88946-63-8; **16b**, 88946-64-9; **17**, 76287-69-9; **18**, 498-66-8; 2,5-norbornadiene, 121-46-0; 1-methyl-1,4-cyclohexadiene, 4313-57-9; bicyclo[4.4.0]deca-1,4-diene, 62690-61-3; 4-methyl-1-cyclohexene, 591-47-9; 4,5-dimethyl-1-cyclohexene, 4300-00-9; 4-phenyl-1-cyclohexene, 4994-16-5.

[1] L. A. Paquette, R. V. Williams, *Tetrahedron Lett. 22* (1981) 4643.
[2] a) P. Radlick, R. Klem, S. Spurlock, J. J. Sims, E. E. van Tamelen, T. Whitesides, *Tetrahedron Lett. 1968*, 5117; b) H. H. Westberg, H. J. Dauben, Jr., *ibid. 1968*, 5123; c) J. H. P. Utley in N. L. Weinberg: *Technique of Electroorganic Synthesis, Part I*, Wiley, New York 1974, p. 873.
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Second Sphere Coordination of Cationic Rhodium Complexes by Dibenzo[3*n*]crown-*n* Ethers**

By *Howard M. Colquhoun, Simon M. Doughty, J. Fraser Stoddart*,* and *David J. Williams*

Dibenzo-crown ethers of the general type DB3*n*C*n* ($n=6-12$) form[1] stable adducts with $[Pt(bpy)(NH_3)_2]^{2\oplus}$ in which the 2,2′-bipyridyl ligand (bpy) participates as a π-acceptor in charge transfer interactions with the benzene rings (π-donors). We have now investigated the structures of 1 : 1 adducts formed between these DB3*n*C*n* receptors[2] and the cationic rhodium(I) complexes[2], $[Rh(cod)(NH_3)_2]^{\oplus}$ and $[Rh(nbd)(NH_3)_2]^{\oplus}$, and discovered that in the case of DB24C8 and DB30C10 the 1,5-cyclooctadiene (cod) and norbornadiene (nbd) ligands also prefer to occupy positions in which they are sandwiched between the two benzene rings of the receptors. In addition to presenting ^{1}H-NMR spectroscopic evidence for this adduct stereochemistry in solution, X-ray structures[3] of the crystalline adducts[2] $[Rh(cod)(NH_3)_2\cdot DB30C10][PF_6]$ **1**, $[Rh(cod)(NH_3)_2\cdot DB24C8][PF_6]$ **2**, and $[Rh(nbd)(NH_3)_2\cdot DB24C8][PF_6]$ **3** provide conclusive proof of a remarkable receptor geometry, clearly much more general in its occurrence than believed previously[1].

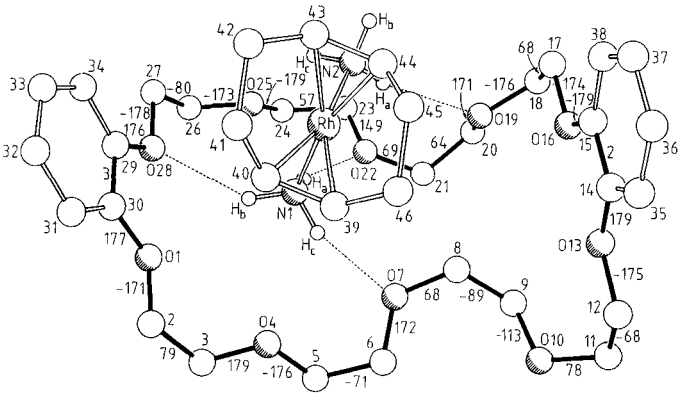

Fig. 1. Structure of the cation of $[Rh(cod)(NH_3)_2\cdot DB30C10][PF_6]$ in the crystal. Torsion angles [°] (O–C–C–O and C–C–O–C) associated with the 30-membered ring are given. Four shortest hydrogen bond distances [Å] [N···O], [H···O], angles [°] between COC planes and HO vectors, and [N–H···O] angles [°]: [N(1)···O(22)]H_a, 3.19, 2.30, 3, 154; [N(1)···O(28)]H_b, 3.16, 2.37, 45, 139; [N(1)···O(7)]H_c, 2.96, 2.06, 42, 155; [N(2)···O(19)]H_a, 3.18, 2.29, 40, 155. Separation [Å] between mean planes of the benzo rings and cod hydrogen atoms: [ring (29/30)···H], H_0 (40), 2.61; H_e (41), 2.98; H_e (42), 3.33; [ring (14/15)···H] H_0 (44), 3.13; H_e (45), 2.87; H_e (46), 3.19.

The solid-state structures (Figs. 1 and 2) of **1**–**3** reveal several surprising features: (a) the preference of the *cis*-NH_3 ligands, without exception, to straddle the side of one of the polyether chains, cf. the solid state structures of $[Pt(bpy)(NH_3)_2\cdot DB3nCn][PF_6]_2$ ($n=8$, 10)[1] which also exhibit this characteristic; (b) the tendency of both NH_3 ligands to underutilize their hydrogen bonding potential towards the polyether chains (only two [N–H···O] distances of less than 3 Å are present in all of the structures), cf. the solid-state structures[4] of transition-metal ammine adducts with 18C6 and DB18C6 where [N–H···O] distances are considerably shorter; and (c) the invariably close juxtaposition of the organic ligands cod and nbd with the benzene rings of DB30C10 and DB24C8, despite the lack of any obvious stabilizing interactions, cf. the charge transfer in $[Pt(bpy)(NH_3)_2\cdot DB3nCn][PF_6]_2$[1]. The distances quoted in Figure 1, together with the three shortest [N–H···O] distances of 3.03, 3.13, and 3.34 Å, and of 2.95, 3.01, and 3.27 Å for **2** and **3**, respectively, suggest that the additive effect of a substantial number of very weak hydrogen bonds and electrostatic interactions confers stability upon the adducts. In both DB24C8 adducts **2** and **3** one of the four phenolic oxymethylene units in the receptor is distorted from its customary coplanarity[1,5] with the benzene ring in order that the O atom can form a hydrogen bond to one of the NH_3 ligands with an approximately trigonal approach to the oxygen atom. It is unclear

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whether adduct stability is enhanced by any attractive interactions[6] between either the cod or the nbd ligands in the complexes and the benzene rings in either DB30C10 or DB24C8 since certain nonbonded atoms only just approach the sum of their van der Waals' radii.

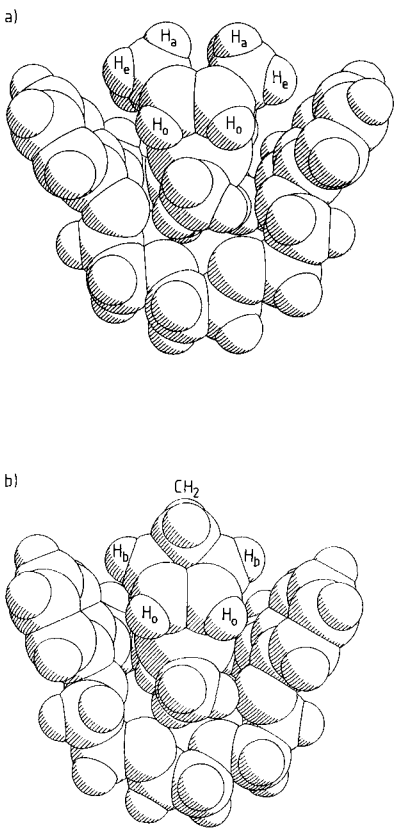

Fig. 2. Computer sketches [(a) and (b)] of space-filling representations of a) $[Rh(cod)(NH_3)_2 \cdot DB24C8]^{\oplus}$ and b) $[Rh(nbd)(NH_3)_2 \cdot DB24C8]^{\oplus}$.

The principal structural features characteristic of the solid state are found to prevail in solution, as judged by the anisotropic diamagnetic shielding effect of the benzene rings upon the chemical shifts of the ^{1}H-NMR signals of cod or nbd ligands. Comparison of the ^{1}H-NMR spectra of $[Rh(L)(NH_3)_2 \cdot DB3nCn][PF_6]$ (L = cod, nbd; $n = 6-12$) with those of the corresponding 1:1 adduct with 18C6 in CD_2Cl_2 reveals substantial upfield shifts for all protons of the cod and nbd ligands (Fig. 3). The shifts assume their greatest magnitude for H_e in the cod ligand and for H_b in the nbd ligand when the receptor is DB24C8. They are accompanied by modest shifts to lower field for the aromatic C_6H_4 protons relative to the singlets observed at $\delta = 6.87-6.90$ for these protons in the free crown ethers. Significantly, this shift also attains its maximum in both series of adducts when the receptor is DB24C8.

Qualitative analysis of nuclear Overhauser effects from difference spectra recorded at 400 MHz confirm that the structure of **2** in CD_2Cl_2 solution is similar to that in the solid state (Fig. 2a). When the signals at $\delta = 1.62$ and 3.54 were irradiated in separate experiments, enhancements of the signal intensities for the C_6H_4 protons at $\delta = 7.03$, as well as for the other cod protons, were observed in both cases. Irradiation of the aromatic protons produced the expected reciprocal effect in the signals at $\delta = 1.62$ and $\delta = 3.54$, but no enhancement in the intensity of the signal at $\delta = 1.41$. These intra- and intermolecular nuclear Overhauser effects also confirm the signal assignments in Figure 3.

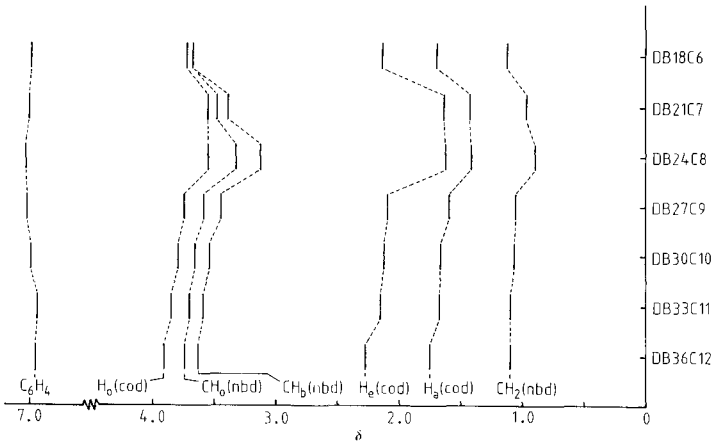

Fig. 3. Partial ^{1}H-NMR line spectra for the complexes $[Rh(cod)(NH_3)_2 \cdot DB3nCn][PF_6]$ and $[Rh(nbd)(NH_3)_2 \cdot DB3nCn][PF_6]$. The ligand protons are designated in Fig. 2 and the signals (singlets) for the benzo-protons refer to $[Rh(cod)(NH_3)_2 \cdot DB3nCn][PF_6]$.

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CAS Registry numbers:
$[Rh(cod)(NH_3)_2 \cdot DB30C10][PF_6]$, 88995-94-2; $[Rh(cod)(NH_3)_2 \cdot DB24C8][PF_6]$, 88995-95-3; $[Rh(nbd)(NH_3)_2 \cdot DB24C8][PF_6]$, 88995-98-6.

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[2] Experimental: The crown ethers DB18C6 and DB24C8 were obtained from Aldrich; DB21C7, DB27C9, DB30C10, DB33C11, and DB36C12 were synthesized by a stepwise procedure (cf. [1]). $[Rh(cod)(NH_3)_2][PF_6]$, m.p. 209–215°, and $[Rh(nbd)(NH_3)_2][PF_6]$, m.p. 159–164°, were prepared from $[Rh(cod)Cl]_2$ (R. B. King, *Organometallic Synthesis 1* (1965) 132) and $[Rh(nbd)Cl]_2$ (E. W. Abel, M. A. Bennett, G. Wilkinson, *J. Chem. Soc. 1959*, 3178), respectively, by treatment of these chloride dimers with NH_3 ($\rho = 0.88$) and then with NH_4PF_6. The crystalline adducts **1**, m.p. 95–100°, **2**, m.p. 135–145°, and **3**, m.p. 118–129°, were obtained by layering Et_2O on top of either CH_2Cl_2 or $(CH_2Cl)_2$ solutions (1:1 stoichiometries). All new crown ethers, complexes, and crystalline adducts gave satisfactory elemental analyses and spectroscopic data.

[3] Crystal data **1**: monoclinic, $a = 9.268(2)$, $b = 34.335(7)$, $c = 13.421(3)$ Å, $\beta = 93.92(2)°$, $V = 4261$ Å^3, space group $P2_1/c$, $Z = 4$, $\rho_c = 1.45$ g cm^{-3}. **2**: monoclinic, $a = 9.195(3)$, $b = 29.380(9)$, $c = 13.900(6)$ Å, $\beta = 93.04(3)°$, $V = 3750$ Å^3, space group $P2_1/c$, $Z = 4$, $\rho_c = 1.49$ g cm^{-3}. **3**: orthorhombic, $a = 15.427(3)$, $b = 18.739(3)$, $c = 25.458(5)$ Å, $V = 7360$ Å^3, space group *Pbca*, $Z = 8$, $\rho_c = 1.49$ g cm^{-3}. Data were measured on a Nicolet R3m diffractometer using the ω-scan routine with graphite-monochromated $Cu_{K\alpha}$ radiation. Structures were solved by the heavy-atom method and refined anisotropically to give R values of 0.034, 0.043, and 0.047, respectively, for 3915, 3401, and 2984 independent observed reflections [$\theta \leq 50°$, $|F_o| > 3\sigma(|F_o|)$]. Further details of the crystal structure investigations can be obtained from the Director of Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.

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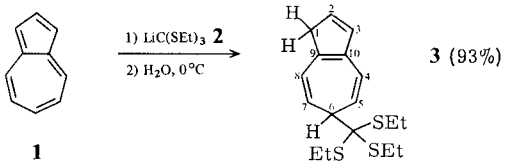
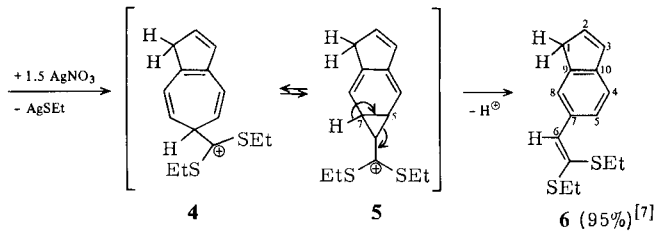
A Novel Rearrangement of the Azulene Skeleton: Ring Contraction of a Dihydroazulene to an Indene Derivative**

By *Siegfried Hünig** and *Burkhard Ort*

Rearrangements of the azulene skeleton predominantly lead to naphthalene derivatives[2]. Herein we describe the first preparative[3] rearrangement which leads via contraction of the seven-membered ring to an indene derivative.

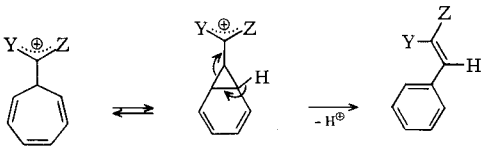
Azulene **1** already reacts at −70 °C in tetrahydrofuran (THF) with the nucleophile **2** generated from triethyl trithioorthoformate[4]. Hydrolysis furnishes a ^{1}H-NMR spectroscopically and chromatographically pure, colorless oil, the 1,6-dihydroazulene derivative **3**[5,6]. When a concentrated solution of silver nitrate in acetonitrile is added dropwise to a solution of **3** in THF, a yellow compound precipitates. Subsequent chromatographic purification of the solution affords 95% 6-[2,2-bis(ethylthio)vinyl]-1*H*-indene **6** as a colorless, undistillable oil[5,7].





Selective decoupling and nuclear Overhauser experiments enable an unambiguous assignment of signals in the ^{1}H-NMR spectrum according to structure **6**[8]. The signals of 1-H_2, 2-H, and 3-H form a A_2MX system, which is almost identical with the corresponding subspectrum of indene[9]. The resonances of the *S*-ethyl groups are very similar, but not exactly the same. The rearrangement is probably initiated by the dissociation of **3** with formation of the cationic cycloheptatriene derivative **4**, which is in equilibrium with the norcaradiene derivative **5**. This finally aromatizes to **6**. If it is assumed that $\delta^\oplus$ charges appear on C-5 or C-7 in the transition state during the cleavage of the three-membered ring, then the regioselective opening to give **6** is understandable: The double bond of the five-membered ring can participate more effectively in the delocalization of the charge if C-5 (and hence C-10) gains $\delta^\oplus$ character.

The transition **5** → **6** is a further example of the cyclopropylmethyl cation/homoallyl cation rearrangement[10], which is realized with several cycloheptatrienes by the reaction sequence **7** → **8** → **9**. However, this rearrangement



7 **8** **9**

only occurs if the carbenium ion is weakly stabilized by Y and Z[11]. The ring contraction in the azulene moiety described here formally appears as a reversal of the classical Plattner azulene synthesis: expansion of the benzene ring in indane by a C_1 unit via a norcaradiene intermediate[12].

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CAS Registry numbers:
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[7] The numbering of the C-atoms of **3** has been used to illustrate the ring contraction.
[8] ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.24, 1.31, 2.83, 2.85 (2 t, 2 d, J = 7.2 Hz; CH_2CH_3), 3.40 (bs; 1-H_2), 6.56 (td, J = 5.6 and 2.0 Hz; 2-H), 6.86 (td, J = 5.6 and 2.0 Hz; 3-H), 7.10 (s; 6-H), 7.35 (d, J = 8.4 Hz; 4-H), 7.53 (d, J = 8.4 Hz; 5-H), 7.81 (bs; 8-H).
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$[S_4N_4]^\oplus[FeCl_4]^\ominus$, a Compound with Cyclic Radical Cation

By *Ulrich Müller**, *Elke Conradi*, *Udo Demant*, and *Kurt Dehnicke*

In contrast to the cyclic sulfur-nitrogen cations such as $S_4N_3^\oplus$[1], $S_4N_4^{2\oplus}$[2], $S_4N_5^\oplus$[3] or $S_5N_5^\oplus$[4] with even numbers of electrons, so far only one radical cation $S_3N_2^\oplus$ has been characterized crystallographically in combination with various anions[5–8]: the lattice contains centrosymmetric dimers with long S···S contacts of about 300 pm.

On separating the products formed in the reaction of $FeCl_3$ with $(NSCl)_3$ in dichloromethane by extraction with CH_2Cl_2, we obtained brown, moisture-sensitive crystals of the composition $S_4N_4FeCl_4$, which according to an X-ray

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structure analysis[9] contain the hitherto unknown radical cation $S_4N_4^{\oplus}$ (Fig. 1). In contrast to the dication $S_4N_4^{2\oplus}$, which occurs as a planar ring (D_{4h} symmetry) with the counterions $SO_3F^{\ominus}$ or $AlCl_4^{\ominus}$ and in the boat conformation (C_{2v}) with the counterion $SbCl_6^{\ominus}$[2], the radical cation $S_4N_4^{\oplus}$ has a puckered eight-membered ring structure in which the S-atoms form an almost ideal square; the N-atoms are located alternately 34, −59, 45, and −38 pm above and below this square. The SN bonds are almost equal in length (average 154 pm), the NSN and SNS angles have mean values of 116.0 and 138.9°, respectively. The SN bond lengths are thus markedly shorter than those in the S_4N_4 molecule (162 pm)[10], but almost the same length as those in the $S_4N_4^{2\oplus}$ cation[2]. The NSN angles in the two cations also differ only slightly ($S_4N_4^{2\oplus}$: average 119°), whereas the SNS angle in the $S_4N_4^{\oplus}$ radical ion, with a value of 139°, is considerably smaller than that in $S_4N_4^{2\oplus}$ (average value 152°[2]).

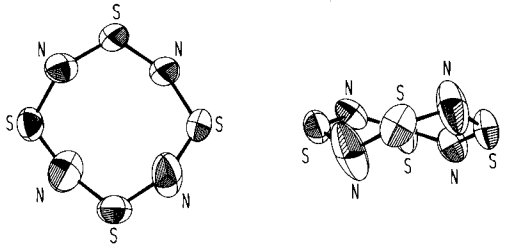

Fig. 1. Structure of the $S_4N_4^{\oplus}$ radical cation (in the crystal of $S_4N_4FeCl_4$) viewed in two directions; ellipsoids of the thermal vibration for 50% probability at 25°C.

The possibility of the presence of $[S_4N_4]^{2\oplus}[FeCl_4]^{2\ominus}$ can be ruled out. The four Fe–Cl bonds in the anion have the same length, namely 219 pm, corresponding exactly to the known value for those in $FeCl_4^{\ominus}$ with various counterions; in $FeCl_4^{2\ominus}$, on the other hand the length is 229 pm[11]. This difference greatly exceeds the limit of error. Equally significant is the IR spectrum: The F_2 stretching vibration of the $FeCl_4^{\ominus}$ anion appears at 388 cm^{-1} (for comparison: $FeCl_4^{\ominus}$ 385 cm^{-1}[12], $FeCl_4^{2\ominus}$ 286 cm^{-1}[13]). Also the IR-active SN stretching vibrations for the $S_4N_4^{\oplus}$ cation were observed at other frequencies than quoted for $S_4N_4^{2\oplus}[S_4N_4(AlCl_4)_2]$: 1091, 1020, 974 cm^{-1}[2]. In accord with the general finding that a smaller positive charge leads to a long-wave shift, the $S_4N_4^{\oplus}$ vibrations appear at 952, 941, 763, 750, and 715 cm^{-1}; the greater number of IR-active vibrations is consistent with the lower C_1 symmetry of the radical cation.

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CAS Registry numbers:
$(NSCl)_3$, 5964-00-1; $[S_4N_4]^{\oplus}[FeCl_4]^{\ominus}$, 88928-89-6.

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[9] Structure determination with 1023 independent, observed reflections, refinement to $R = 0.046$; $Mo_{K\alpha}$ radiation, four-circle diffractometer, Enraf-Nonius (Delft); crystallographic data: $a = 803$, $b = 1004$, $c = 1509$ pm, $\beta = 104.7°$, space group $P2_1/c$, $Z = 4$. Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD 50664, the names of the authors, and full citation of the journal.
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Molecular Structure of 8,11-Dichloro[5]metacyclophane: A Strongly Bent Benzene Ring**

By *Leonardus W. Jenneskens, Johannes C. Klamer, Henricus J. R. de Boer, Willem H. de Wolf, Friedrich Bickelhaupt**, and *Caspar H. Stam*

Of particular interest in the chemistry of the [n]para-[1] and [n]metacyclophanes[2] with short oligomethylene bridges, is the high strain and its effect on the geometry and reactivity of such compounds. Thus, it is conceivable that the sterically enforced bending of the benzene ring could lead to a bond fixation tending towards a cyclohexatriene structure; the increased tendency of some cyclophanes to undergo Diels-Alder reactions has come under discussion in this sense[2d,3]. 8,11-Dichloro[5]metacyclophane **1** is a representative of the meta series with the hitherto shortest bridge[4].

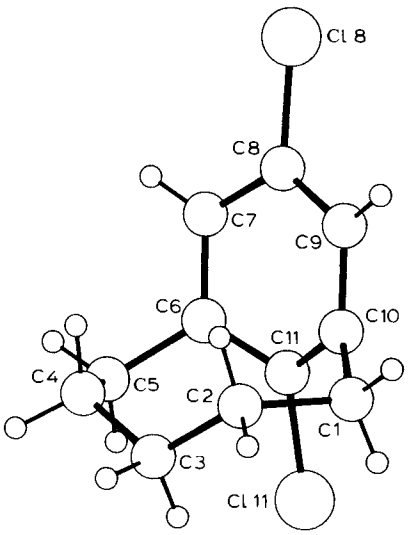

Fig. 1. PLUTO diagram of the structure of **1** in the crystal [5]. Selected bond lengths [Å] and angles [°]: C1–C2 1.569(3), C1–C10 1.506(3), C2–C3 1.566(3), C8–C9 1.389(3), C9–C10 1.400(3), C10–C11 1.391(2), C8–Cl8 1.747(3), C11–Cl11 1.754(3); C2–C1–C10 104.7(2), C1–C2–C3 121.9(2), C2–C3–C4 122.2(2), C7–C8–C9 120.3(3), C7–C8–Cl8 119.5(2), C8–C9–C10 118.8(2), C1–C10–C9 121.8(2), C1–C10–C11 114.8(2), C9–C10–C11 117.4(2), C6–C11–C10 118.7(2), C6–C11–Cl11 119.7.

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In the crystal, the molecule has C_s symmetry (Fig. 1); its conformation essentially corresponds to that which, according to MNDO calculations and NMR data, is the more stable of the two conformations in solution[2f]. The benzene ring has an unsymmetric boat conformation, whose most striking characteristic is the marked bending of the "bow" (Fig. 2; $\alpha_1 = 26.8°$); to our knowledge this is the strongest deviation from planarity known so far in a benzene ring. The angle at the "stern" is smaller ($\alpha_2 = 12°$), and the sum $\alpha_1 + \alpha_2 = 38.8°$ is close to that found in the [6]paracyclophane system (41.3°[1a], 38.9°[1b]). A remarkable feature is the large angle $\beta_1 = 48°$; the strain at the bridgehead carbon atoms C-6 and C-10 also manifests itself in marked pyramidalization (sum of the bond angles: 354°).

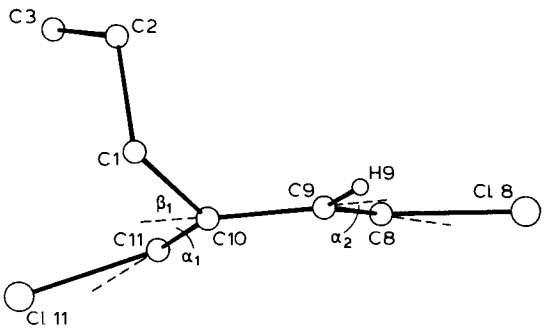

Fig. 2. Side view of the structure of **1** in the crystal [5]. α_1, α_2, β_1, see text.

As has already been observed on several occasions with cyclophanes[6] and acyclic, strongly crowded benzene derivatives[7], the boat conformation is preferred over the—sterically possible—chair conformation. Perhaps this is due to the more favorable π-overlap in the boat form[6b, 7]. This effect also explains the striking finding that all six atoms bound to the benzene ring lie on the same side of the ring, namely the convex side, whereas the substituents in paracyclophynes are, for the same reason, tilted to the concave side[8]. Exceptions to this rule are apparently only found when steric factors counteract such an arrangement, as in the case of the phosphorus atom in bis(2,4,6-tri-*tert*-butylphenyl)phosphinic chloride[7].

The bending of the benzene ring manifests itself in an adjustment of the bond angles in the ring, particularly at C-6, C-10, and C-11. In contrast, the bond lengths in the benzene ring are, surprisingly, completely normal (mean value 1.393 ± 0.007 A). On the basis of this criterion, one must conclude that the aromaticity of the ring is essentially intact. This hypothesis is supported by the ring current effect in the NMR spectra[2f]. These findings are not reconcilable with the postulated cyclohexatriene character, which was considered to explain the high Diels-Alder reactivity[2d, 3]. Apparently, the destabilization of the aromatic ring, which is reflected both in the chemical reactivity and in the UV spectrum[2b, e], is not caused by (partial) bond fixation.

The pentamethylene bridge consists of sp^3-hybridized carbon atoms and is therefore less rigid than the aromatic ring. Consequently, the effects of strain are discernible in the bond lengths as well as in the bond angles. The trend is similar to that in the short-chain [n]paracyclophanes[1]. The angle at the benzylic carbon atom is remarkably small (C10–C1–C2 = 104.7°); the angles at the other bridge atoms (ca. 122°) and the CC bond lengths (1.56–1.57 Å) are somewhat larger than in the [6]paracyclophane system[1b].

Finally, we would like to point out that the MNDO calculations[2f] have predicted the geometry of **1** remarkably well, even though they are not perfect in detail (e.g. $\alpha_1 = 32$, $\alpha_2 = 9$, $\beta_1 = 41°$).

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[4] In the non-benzenoid series, a [4]metatroponophane has been described: Y. Fujise, T. Shiokawa, Y. Mazaki, Y. Fukazawa, M. Fujii, S. Ito, *Tetrahedron Lett. 23* (1982) 1601.

[5] Crystallographic data for **1**: Space group Pbnm; $a = 9.399(2)$, $b = 11.832(3)$, $c = 9.176(2)$ Å; $Z = 4$. Nonius CAD4 diffractometer, $Cu_{K\alpha}$ radiation, graphite monochromator; 864 observed reflections ($I > 2.5\sigma(I)$), no absorption correction. The structure was determined by the heavy atom method and refined by block-diagonal least squares calculations (anisotropic for C and Cl, isotropic for H) to $R = 0.031$. A weighting $w = 1/(6.1 + F_0 + 0.01 F_0^2)$ was applied and an extinction correction performed. Anomalous scattering of the chlorine was taken into account.—Further details of the crystal structure investigation are available on request from the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW (England).

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syn-Diastereoselective Homoaldol Reactions: γ-Hydroxyalkylation of (*Z*)-2-Butenyl Carbamates and Synthesis of β,γ-*cis*-Di- and -Trisubstituted γ-Lactones**

By *Dieter Hoppe** and *Florian Lichtenberg*

Diastereoselective homoaldol reactions[1]—they correspond to the hydroxyalkylation of homoenolate ions[2] to give γ-aldols **3**—were first reported very recently. However, the approaches described so far only permit access to *anti*[3,4]-diastereomers **3**[1]. We have now been able to accomplish the first *syn*[3,4]-selective version of the homoaldol reaction, starting from the (*Z*)-2-butenyl carbamate *Z*-**6**.

The *anti*-selective procedures utilize, e.g., α-metalated (*E*)-2-butenyl carbamates[1a–c] *E*-**4a**, (*E*)-2-butenyl ethers *E*-**4b**[1d] or *E*-**4c**[1e], and (*E*)-2-butenylsilanes[1f] *E*-**4d** as homoenolate reagents; the sequences proceed via 1-function-

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Table 1. Regioisomeric and diastereomeric ratios in the synthesis of 1-alkenyl carbamates **10**.

Educts 1 and 12		R^1	R^2	Product [a]	Yield [b] [%]	Diastereomeric ratios **10** [c] *E-syn* : *Z-syn* : *E-anti* : *Z-anti*				*syn* : *anti*	**10** : **11** [c] (γ : α)
1a	**12a**	CH_3	H	**10a** [d]	81	88	6	1	5	94 : 6	94 : 6
	12b				88	87	3	8	2	90 : 10	99 : 1
1b	**12a**	$(CH_2)_3CH_3$	H	**10b**	84	79	6	8	7	85 : 15	89 : 11
1c	**12a**	$CH(CH_3)_2$	H	**10c**	88	80	6	7	7	86 : 14	93 : 7
	12b				90	78	9	1	12	87 : 13	99 : 1
1d	**12a**	$C(CH_3)_3$	H	**10d**	90	80	6	9	5	86 : 14	95 : 5
1e	**12b**	(*E*)-$CH{=}CHCH_3$	H	**10e**	91	68	18	3	11	86 : 14	99 : 1
1f	**12b**	C_6H_5	CH_3	**10f**	71	72	10	1	17	82 : 18	92 : 9
1g	**12b**	CO_2CH_3	CH_3	**10g**	67 [e]	81	6	1	12	87 : 13	92 : 8

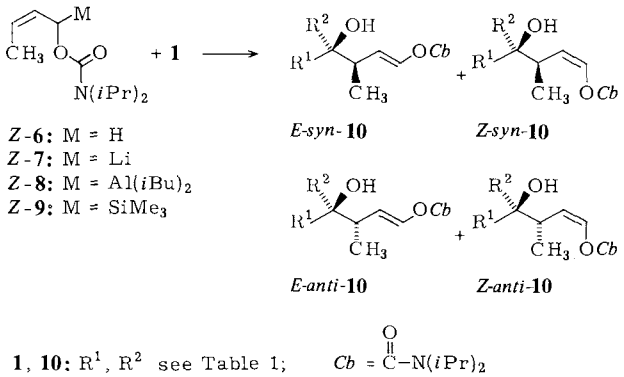
[a] Correct C,H analyses (±0.3%). [b] Diastereomeric mixture **10** after purification by medium-pressure chromatography. [c] In the crude product, determined by capillary chromatography (quartz column SE 30, 50 m, H_2, temperature program 100–230°C, 5–8°C/min); sequence of elution: **11** (diastereomers), *Z-anti*, *Z-syn*-, *E-anti*-, *E-syn*-**10**. [d] Diastereomeric ratio of **10a** achieved with *Z*-**7** : 47 : 15 : 17 : 21; *syn*/*anti* = 62 : 38. [e] Yield of pure *E-syn*-**10a** after recrystallization from pentane, m.p. 76°C.

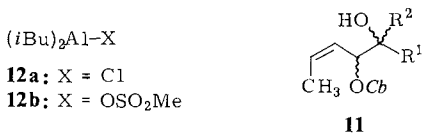
alized 4-hydroxyalkenes[3] of the type *anti*-**5**. *Z*-Configurated derivatives **4** should—as long as the addition of **1** proceeds via a pericyclic transition state with allylic inversion[5]—predominantly yield the racemic[3] diastereomers *syn*-**5**[6]. The problem is the regio- and stereoselective generation of metal compounds of the type *Z*-**4**.

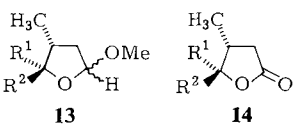
The following procedure proved to be successful: *Z*-**6**[7] is deprotonated with *n*-butyllithium (in pentane, 1.1 equiv. TMEDA, 30 min at −78°C)[2a] to give *Z*-**7**. To check its configurational stability and the α-selectivity of the metal exchange, the solution of *Z*-**7** was kept at −78°C for 2 h and then quenched with chlorotrimethylsilane: the silane *Z*-**9** was formed (yield 95%; <5% *E*-**9**)[8]. Conversely, *E*-**6** afforded pure *E*-**9**[8]. Thus, the lithium compounds **7** prove to be surprisingly stable against torsion of the β,γ-bond.

By exchange[9] of the cation in *Z*-**7** with diisobutylaluminum chloride[1a] (**12a**) or methanesulfonate[10] (**12b**) the alane *Z*-**8** is formed, which adds aldehydes **1** or prochiral ketones **1** (such as acetophenone **1f** or methyl pyruvate **1g**) to give predominantly the diastereomers[3,12] *E-syn*-**10** (see Table 1). Noteworthy is the high γ-regioselectivity of the mesylate procedure[13]: in this way, with aldehydes **1a–e** competing formation of the α-adducts **11** often amounts to <1%.

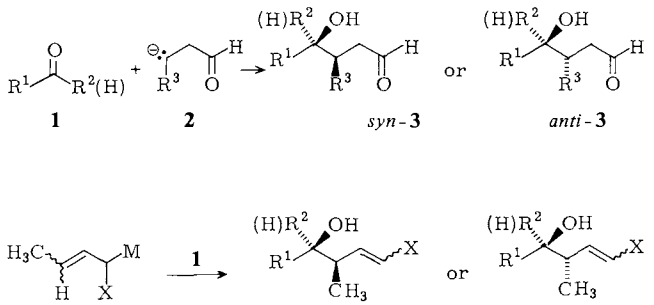
The mercury(II) acetate-catalyzed methanolysis[1a,c] of *syn*-**10** proceeds—as was observed for the *anti*-diastereomers **10**[1c]—with retention of the relative configurations at C-3 and C-4, and affords the *cis*-γ-lactol methyl ethers **13** (yield ca. 90%). Subsequent Grieco-oxidation[14,15] yields β,γ-*cis*-substituted γ-lactones **14**. Thus *E*/*Z*-*syn*-**10b** furnishes (±)-quercus-lactone b[16] **14b** (yield 84%) and *E-syn*-**10g** the (±)-"*trans*"-methyl crobarbate[17] **14g** (yield 67%).







13b, **14b**: $R^1 = (CH_2)_3CH_3$, $R^2 = H$
13g, **14g**: $R^1 = CO_2Me$, $R^2 = CH_3$



4a: M = Al(*i*Bu)$_2$, Ti(NEt$_2$)$_3$ etc., X = OC(O)N(*i*Pr)$_2$ — *syn*-**5** / *anti*-**5**
4b: M = $SnBu_3$, X = OCH_2OMe
4c: M = Ti(C_5H_5)$_2$, X = OPh
4d: M = BR_2, X = $SiMe_3$

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[3] All compounds are racemic; one enantiomer is arbitrarily shown for the characterization of the relative configurations.

[4] It is impossible, on the basis of the CIP system, to characterize the relative configurations of diastereomers in general formulas. Therefore, ac-

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cording to Masamune [4a], we use the prefixes *syn* and *anti* to distinguish members of the two diastereomeric series; if necessary they are to be defined by structural formulas. *syn*-**10** is formed on approach of reactants with the relative topicity *ul* [4b]; *anti*-**10** is formed in a *lk* process [4b] (this applies here, because R^1 always has a higher CIP priority than R^2; cf. Table 1).—a) S. Masamune, S. A. Ali, D. L. Snitman, D. S. Garvey, *Angew. Chem. 92* (1980) 573; *Angew. Chem. Int. Ed. Engl. 19* (1980) 557; b) D. Seebach, V. Prelog, *ibid. 94* (1982) 696 and *21* (1982) 654; c) cf. also D. Hoppe, *Nachr. Chem. Tech. Lab. 30* (1982) 1030.

[5] Reviews: a) R. W. Hoffmann, *Angew. Chem. 94* (1982) 569; *Angew. Chem. Int. Ed. Engl. 21* (1982) 555; b) Y. Yamamoto, K. Maruyama, *Heterocycles 18* (1982) 845.

[6] A *syn*-selective synthesis of 1-alkenyldithiocarbamates (*syn*-**5**, $X=SC(S)NMe_2$) has been reported, however hydrolysis to give **3** remains an unsolved problem; cf. T. Hayashi, N. Fujitaka, T. Oishi, T. Takeshima, *Tetrahedron Lett. 21* (1980) 303.

[7] *Z*-**6** (<2% *E*-**6**) was obtained by hydrogenation of the corresponding 2-butynyl carbamate with "P-2-nickel" catalyst/ethylenediamine; cf. C. A. Brown, V. K. Ahuja, *J. Chem. Soc. Chem. Commun. 1973,* 553.

[8] ^{13}C-NMR ($CDCl_3$, δ): *Z*-**9**: 13.60, *E*-**9**: 17.95 (4-CH_3).

[9] For the *syn*-selective carbonyl addition of (*Z*)-butenyldiethylalane, cf. D. B. Collum, J. H. McDonald III, W. C. Still, *J. Am. Chem. Soc. 102* (1980) 2118.

[10] In each case **12b** was freshly prepared from equimolar amounts of diisobutylaluminum hydride and methanesulfonic acid as a 0.25 M solution in hexane/ether (1:3).

[11] General procedure: A 1.6 M solution of *n*-butyllithium (5.5 mmol) in hexane is added dropwise to a solution of *Z*-**6** (5.0 mmol) and tetramethylenediamine (TMEDA) (5.5 mmol) in pentane (15 mL) at $<-70°C$ under N_2. The resulting suspension is stirred for 30 min and then treated with 5.5 mmol **12a** (ca. 25% in toluene) or **12b** [10]. After 1.5 hours' vigorous stirring at $<-70°C$, 5.5 mmol **1** is injected into the mixture and stirring continued for a further 1—3 h (**10f**: 16 h) at $-78°C$. The mixture is then treated with acetic acid (50 mmol), warmed to 0°C, extracted with 50 mL 10% sodium potassium tartrate solution and with 50 mL ether, and worked-up in the usual way [1a]. Isolation of **10** by medium-pressure chromatography on silica gel (ether/petroleum ether).

[12] The stereochemical assignment is confirmed by degradation to known 3-hydroxyalkanoic acids (**10a**, **10d**) [1a] or by conversion into known γ-lactones (**10b** [16], **10f** [1c], **10g** [1f, 17]).

[13] We ascribe the improved regioselectivity with **12b** to increased α-selectivity of the Li/Al exchange.—**12a** reacts with lithiated 2-butenyl ethers to give γ-alanes; cf. M. Koreeda, Y. Tanaka, *J. Chem. Soc. Chem. Commun. 1982,* 845.

[14] P. A. Grieco, T. Oguri, Y. Yokoyama, *Tetrahedron Lett. 1978,* 419.

[15] For experimental procedure and list of references to γ-lactone syntheses see [1c].

[16] M. Masuda, K. Nishimura, *Chem. Lett. 1981,* 1333; and references cited therein.

[17] J. Huang, J. Meinwald, *J. Am. Chem. Soc. 103* (1981) 861; and references cited therein—for synthesis of "*cis*"-**14g**: [1f].

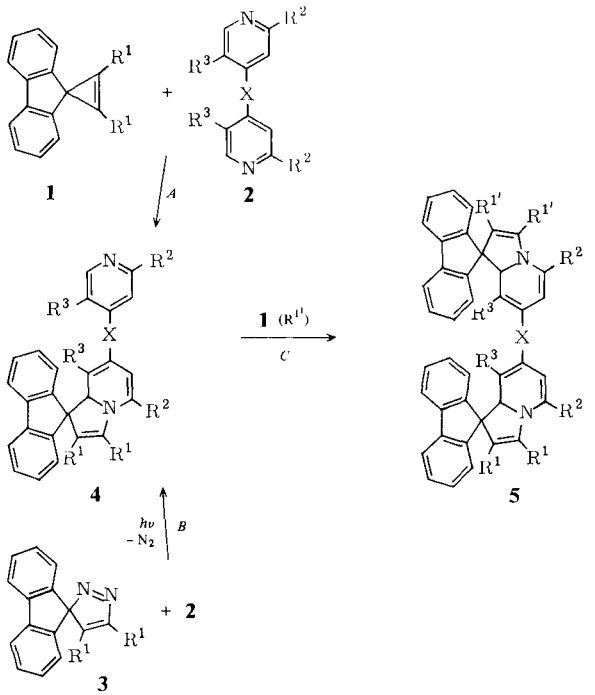
Tailor-Made Photochromic Systems: First Bichromophoric Spiro-1,8a-dihydroindolizines**

By *Peter Spang* and *Heinz Dürr**

Photochromic compounds have attracted a great deal of interest in recent years, largely because they can serve as materials for optical display and data logging[1], as actinometer substances and light filters[2], as well as for solar energy conversion[3]. It has recently been reported that they also appear to be suitable for the frequency-doubling of lasers[3b]. Such applications call for photochromic systems in which long wave absorption ranges, high storage densities, the combination of two colors, and slow or rapid systems can be obtained in a *selective way.*

We have already reported on the photochromic system of the spiro-1,8a-dihydroindolizines[4]. Herein we describe the novel bichromophoric systems **5**, which consist of two 1,8a-dihydroindolizine units, and outline their synthesis and spectroscopic properties.

The bichromophoric species **5** were synthesized by reaction of electrophilic spirocyclopropenes **1** with the bipyridines **2** (X = nothing), 4,4′-ethylenedipyridines **2** ($X=-CH_2-CH_2-$), or 4,4′-vinylenedipyridines **2** (X = −CH=CH−) in the molar ratio 1:1 in ether in the absence of light at room temperature. These reactions afforded mixtures of the yellow 1:1 adducts **4** and the yellow to yellowish orange 2:1 adducts **5** (Table 1), which could easily be separated by column chromatography and recrystallized from ether/*n*-pentane (route *A*). When the molar ratio of the reactants was adjusted to 2:1 the bichromophores **5** were obtained in quantitative yields. Compounds **5** could also be prepared by reaction of **4** and equimolar amounts of **1** (route *C*). Systems containing two different spirodihydroindolizine moieties are accessible via route *C*; these may prove very interesting from the technical point of view. In the case of the thermally unstable spirocyclopropenes **1**, the 1:1 adducts **4** could be synthesized by direct photolysis of the spiro-3*H*-pyrazoles **3** in a 1% ethereal solution of **2** (route *B*)[4].



Reactions *A*—*C* also lead to the formation of betaines[4] as dark colored intermediates which spontaneously cyclize thermally to give the products **4** and **5**. On irradiation (UV/VIS), **5** and **4** undergo electrocyclic ring cleavage with regeneration of the betaines **6** (Table 1) and the analogous intermediates of **4**, respectively. Assignment of the structures of **4** and **5** was possible from the ^1H-NMR, IR, UV, and mass spectroscopic data. The ^1H-NMR data of **5a–f** indicate a symmetric structure. The absorption maxima of **5a–f** lie between 381 and 420 nm, those of the colored forms **6a–f** between 575 and 702 nm. As in the case of the known bichromophoric spiropyran compounds[5], the maxima are markedly broadened in the visible region.

The finding that the extinction coefficients of **5** are about double those of the corresponding coefficients of **4**

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Table 1. Some data of the 2:1 adducts **5** and **6**. E = CO_2CH_3. UV data determined at 20°C in CH_2Cl_2.

	R^1	$R^{1'}$	X	R^2	R^3	Yield [%]	M.p. [°C]	**5** λ_{max} [nm]	$\varepsilon \times 10^3$	**6** λ_{max} [nm]	**6**→**5** $k \times 10^{-3}$ [s^{-1}]
a	E	E	—	H	H	39	218	396	20.4	630	6.7
b	Ac	Ac	—	H	H	48	160	420	13.6	575	1.7
c	E	E	—	Me	H	75	220	396	20.9	628	2.1
d	E	E	—	H	Me	69	192	399	14.5	623	17.8
e	E	E	$(CH_2)_2$	H	H	48	126	381	24.6	596	6.9
f	E	E	$(CH)_2$	H	H	73	186	394	15.1	702	4.6
g	E	Ac	—	H	H	37	188	407	16.7	585	2.5
h	E	Ac	—	Me	H	28	138	404	22.3	590	9.0
i	E	Ac	$(CH)_2$	H	H	58	162	401	23.8	650	1.3

suggests the presence of two independent chromophores with additive character in **5**. Thus, the colored forms **6g–i** of the unsymmetric compounds **5g–i** show only one broad maximum, which is centered between the maxima of the corresponding precursors **4**. This long-wave absorption maximum of **6g–i** decreases in the reaction **6**→**5** with a rate constant k which roughly corresponds to the mean value of k in the reaction of the subsystems. In all cases, the rate of the thermal cyclization **6**→**5** is first order. The UV spectroscopic behavior of the unsymmetric species **5g–i** indicates that both spiro systems participate in the photochromism of **5**, i.e. that both dihydropyrrole rings open in an electrocyclic process; this photochromically induced [4n+2]-reaction follows a conrotatory mode.

Thus, **4a** reacts with the spirocyclopropene **1b** (R^1 = Ac) according to route *C*, initially furnishing the red monobetaine **7g** (absorption at λ_{max} = 549 nm), which can be converted by irradiation with light of wavelength 396 nm (λ_1) into the dibetaine **6g** (λ_{max} = 585 nm). Reaction of **4b** with **1a** ($R^1 = CO_2CH_3$), on the other hand, leads to the green monobetaine **7g'** (λ_{max} = 645 nm), which likewise reacts further on irradiation with light of wavelength 420 nm (λ_2) to give **6g**, which thermally recyclizes to **5g**.

The activation parameters of the thermal cyclization **6**→**5** (in CH_2Cl_2 at 25°C) determined by UV have the following values: $\Delta G^{\neq}$ = 16.4–20.3 kcal/mol, $\Delta H^{\neq}$ = 4.2–17.9 kcal/mol, $\Delta S^{\neq}$ = −11.7 to 40.9 cal mol^{-1} K^{-1}.

Thus, molecules with "tailor-made" spectroscopic properties have been synthesized for the first time in the dihydroindolizine series. The selective opening of a particular ring in unsymmetrically substituted compounds **5** is possible by selective monochromatic excitation. These special properties open up a wide spectrum of possible practical applications.

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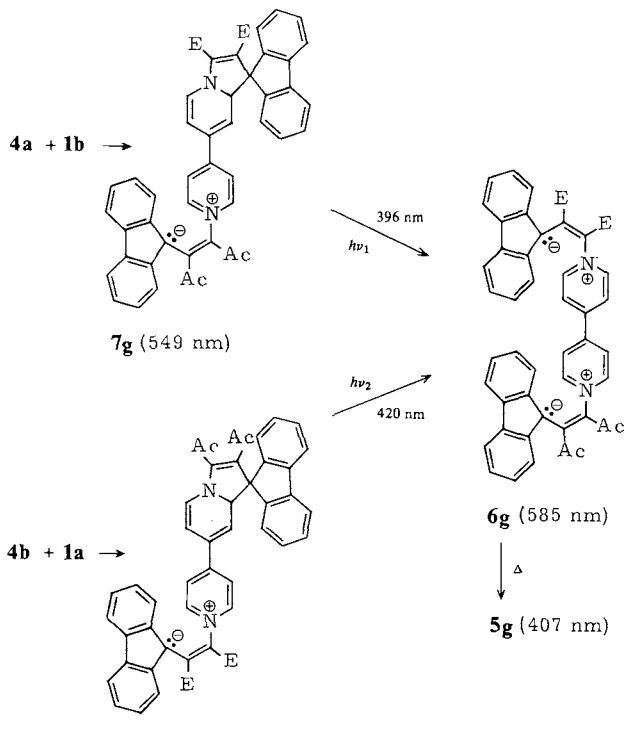

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Synthesis of 1,2:3,4:5,6-Trianhydrohexitols with *gluco-*, *manno-*, and *ido*-Configuration**

By *Peter Köll**, *Michael Oelting*, and *Jürgen Kopf*

Dedicated to Professor Kurt Heyns on the occasion of his 75th birthday

Diepoxides of tetritols and hexitols can act both carcinogenically as well as tumorstatically[1]. The physiological action strongly depends on the configuration of the isomer[2,3]. Although these diepoxides have been the subject of intensive studies, to our knowledge the related triepoxides of hexitols have so far never been prepared.

In connection with the preparation of other trianhydrides of hexitols[4], we have now synthesized and characterized for the first time some of the ten possible isomers (four enantiomeric pairs, two *meso* compounds). As starting substances we used the (*E*)-1,2:5,6-dianhydro-3,4-dideoxy-3-hexenitols **1** and **4** with D-*threo*- or *erythro*-configuration described by *Kuszman* and *Sohár*; **1** and **4** are readily accessible in several steps from D-mannitol and D-glucitol, respectively[5]. However, on attempting to synthesize the title compounds by reaction of **1** and **4** with *m*-chloroperbenzoic acid considerable decomposition occurred. Payne epoxidation[6] with H_2O_2 in methanol in the

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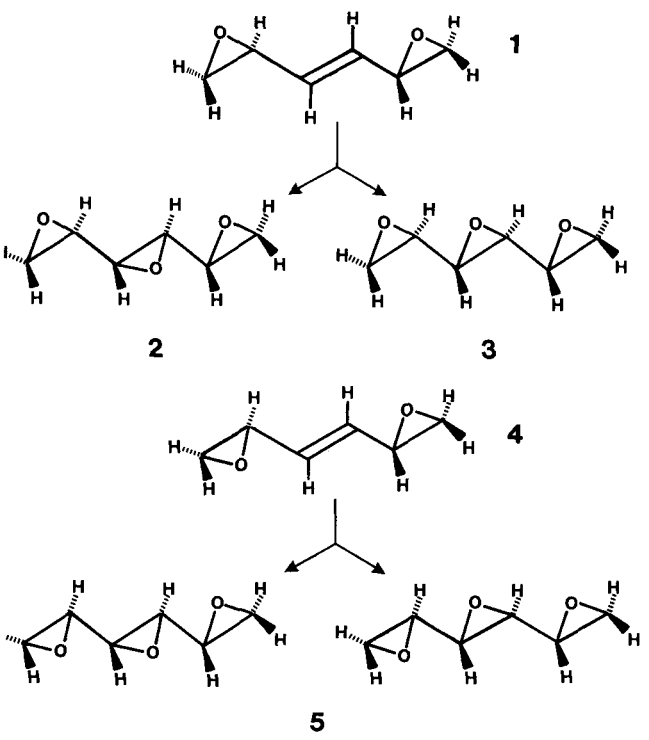
presence of acetonitrile or trichloroacetonitrile[7], on the other hand, led in the case of the D-*threo* isomer **1** to a 1:3 mixture of two enantiomerically pure diastereomers **2** and **3** in 81% yield, having D-*manno*- or D-*ido*-configuration. Both crystallized out after chromatographic separation.



As expected, on epoxidation of the *erythro*-alkene **4** only one optically inactive product is isolable, namely the racemic trianhydroglucitol **5**[8].

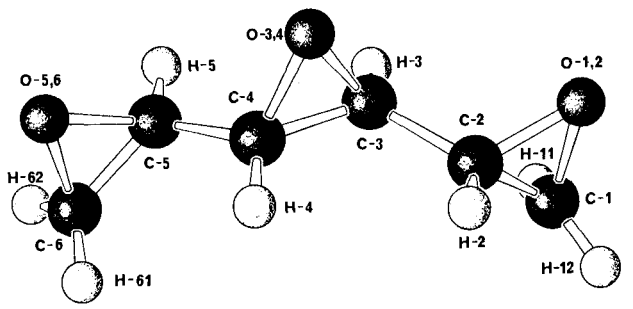


Fig. 1. SCHAKAL diagram [10] of the asymmetric unit of **3**: space group $P2_12_12_1$, $a=460.5(4)$, $b=909.4(7)$, $c=1534.8(9)$ pm, $Z=4$; 912 independent reflections ($I>3\sigma(I)$), $R=0.050$, $R_w=0.027$.—Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD 50655, the names of the authors, and the journal citation.

The triepoxide structure of the compounds isolated was confirmed by elemental analysis, NMR data, and mass spectroscopy. Moreover, **2** and **3** showed optical activity[9]. However, an unequivocal assignment of configuration was impossible on the basis of this data alone. But a subsequent X-ray structure analysis showed that **3** has the *ido*-configuration, and consequently **2** the D-*manno* configuration. As shown in Figure 1, 1,2:3,4:5,6-trianhydro-D-iditol **3** assumes a crescent shaped conformation with favorable *gauche* orientation of the oxygen atoms. Such an arrangement would also be possible in the alternative zig-zag conformation; in fact, the low values of the coupling constants $J_{2,3}=J_{4,5}=4.4$ Hz indicate that this conformation is adopted in solution too. A much greater value would be expected for the pure bent conformation.

A mixture of the 1,2:3,4:5,6-trianhydrohexitols with *gluco*-, *manno*-, and *ido*-configuration is also obtained when commercially available 1,3,5-hexatriene[11] (ca. 70% *E*- and ca. 30% *Z*-isomer) is oxidized as described above. The reaction is much slower and only racemates are obtained: The DL-*gluco*:DL-*manno*:DL-*ido* ratio is 2:1:4 (overall yield 13% referred to hexatriene used in the reaction).

Small amounts of three further isomers are also obtained; these are presumably formed by triepoxidation of *Z*-hexatriene. The main component could be separated by crystallization (m.p. 80°C). The symmetric ^{13}C-NMR spectrum and the observed polarity indicated this as being 1,2:3,4:5,6-trianhydro-*meso*-galactitol. The other two, as yet preparatively unisolable isomers must have the *meso-allo*- and DL-*altro*-configurations.

Finally, it should be pointed out that the isomeric 1,2:3,4:5,6-trianhydroinositols ("benzene triepoxides") derived from cyclohexane (or benzene) have been known for some time[12].

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[8] *Experimental:* Preparation of **2** and **3**: A mixture of **1** [5] (133 mg), methanol (10 mL), $KHCO_3$ (10 mg), acetonitrile (7.6 mL), and H_2O_2 (8.5 mL) was stirred for 2.5 d at RT, treated with 25 mL saturated NaCl solution, and extracted portionwise 5 times with a total of 50 mL CH_2Cl_2. The organic phase was evaporated to dryness in vacuo and the resulting syrup subjected to column chromatographic separation (silica gel 60; ether as eluent): fraction 1 ($R_F=0.8$) 34 mg (22%) **2**; fraction 2 ($R_F=0.7$) 89 mg (59%) **3**; crystallization of both fractions from ether/hexane.—*rac*-**5**: Using the same procedure 150 mg **4** [5] furnished 100 mg (58%) *rac*-**5** as a syrup; $R_F=0.74$ in ether.—Triepoxidation of 1,3,5-hexatriene (365 mg) was carried out analogously to that of **1**. Separation of the components was accomplished on silica gel 60 using ethyl acetate/CCl_4 (1:3) as eluent. Fraction 1 ($R_F=0.49$) 10 mg (2%) *rac*-**2**; fraction 2 ($R_F=0.41$) 22 mg (4%) *rac*-**5**; fraction 3 ($R_F=0.31$) 39 mg (7%) *rac*-**3** (this fraction contained small amounts of an as yet, unknown isomer).
[9] Physical data: **2**: m.p. 36—37°C; $[\alpha]_D$ +22.7 ($c=1.1$ in $CHCl_3$); ^{1}H-NMR (400 MHz in $CDCl_3$): $\delta=3.01$ (m, H-2,3,4,5), 2.86 (q, H-1,6), 2.71 (q, H-1′,6′); $J_{1,1'}=J_{6,6'}=5.0$, $J_{1,2}=J_{5,6}=2.4$, $J_{1',2}=J_{5,6'}=3.8$ Hz.—**3**: m.p. 51—52°C; $[\alpha]_D$ −49.3 ($c=1.0$ in $CHCl_3$); ^{1}H-NMR (400 MHz in $CDCl_3$): $\delta=3.02$ (s, H-2,3,4,5), 2.84 (q, H-1,6), 2.76 (q, H-1′,6′); (400 MHz in C_6D_6): $\delta=2.81$ (d, H-3,4), 2.75 (m, H-2,5), 2.57 (q, H-1,6), 2.53 (q, H-1′,6′); $J_{1,1'}=J_{6,6'}=5.4$, $J_{1,2}=J_{5,6}=4.0$, $J_{1',2}=J_{5,6'}=2.6$, $J_{2,3}=J_{4,5}=4.4$ Hz.—*rac*-**5**: syrup; $[\alpha]_D$ 0; ^{1}H-NMR (80 MHz in $CDCl_3$): $\delta=2.68-3.00$ (m, 8H). The mass spectrum showed decomposition profiles analogous to those in the other isomers.
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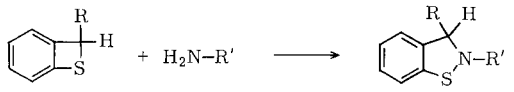
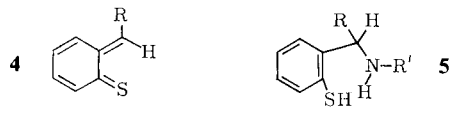
Ring Expansion of Benzothiete to 2,3-Dihydrobenz[*d*]isothiazoles**

By *Kuppusamy Kanakarajan* and *Herbert Meier**

The 2,3-dihydrobenz[*d*]isothiazole (2,3-dihydro-1,2-benzisothiazole) system has acquired special importance through the saccharin molecule[1] and the popular artificial sweeteners that have been developed in recent years[2]. However, very little is known about either the parent compound or the simple (unoxidized) derivatives. We have now discovered a completely new synthetic route to this class of compounds. It belongs to the important class of ring expansion reactions in the synthesis of heterocycles[3]. The starting compounds are the readily accessible[4,5] benzothietes **1**, R = H, CO_2CH_3. Reaction of **1** with primary amines in boiling toluene furnishes the 2,3-dihydro-1,2-benzisothiazoles **3** in good yields (Table 1).



1 **2** **3**

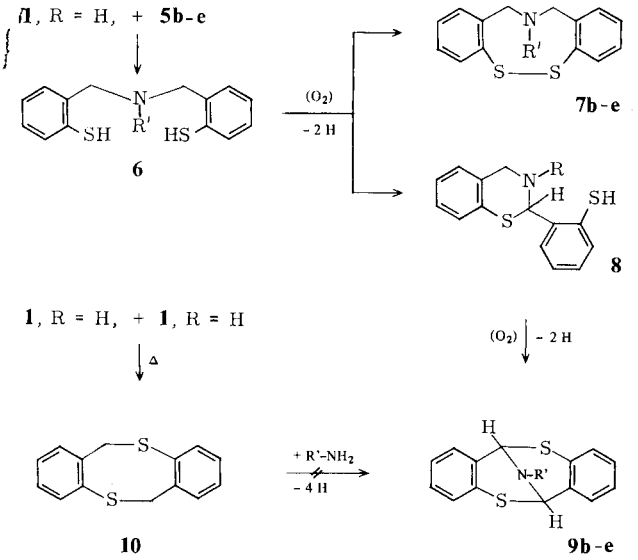


4 **5**

After thermal opening of the four-membered ring in **1** to give the *o*-quinoid system **4**, a 1,4-(or 1,8-)addition takes place, resulting in formation of **5**. A renewed ring closure in the last step follows by autoxidation. The molar ratio of **1** and **2** used in this reaction is 1:4. With a molar ratio of 1:1 the yield of **3** decreases in favor of *N*-substituted 12,13-dihydro-11*H*-dibenzo[*c,h*][1,2,6]dithiazonines **7** and 6,12-dihydro-6,12-iminodibenzo[*b,f*][1,5]dithiocines **9**, a reaction we have monitored in the case of **b–e** (Table 1).

Formation of **9** via the dimer **10** obtained on heating[5] can be ruled out. Heterocycles of type **7** were hitherto unknown, whereas the bridged systems **9** have already been described in the literature as products of the reaction of *o*-mercaptobenzaldehyde with amines[6].

In order to establish the scope of the ring expansion reaction, the higher boiling benzylamine was used in example **f**, while a substituted benzothiete was used in example **g**. The 2,3-dihydrobenz[*d*]isothiazoles **3a–g**, which were isolated by column chromatography on silica gel with petroleum ether 60–90/toluene (2:1), are analytically pure liquids which partially decompose on attempted distillation. In the ^{1}H- and ^{13}C-NMR spectroscopic characterization, the position 3 is the most interesting. During the ring expansion to **3**, the NMR signals shift about 0.1–0.2 and 9–12 ppm, respectively, downfield compared to those of benzothiete **1**, R = H (δ(2-H) = 4.27 and δ(C-2) = 36.5) or methyl benzothiete-2-carboxylate **1**, R = CO_2CH_3 (δ(2-H) = 5.17 and δ(C-2) = 49.2).



6 **7b–e** **8** **10** **9b–e**

Table 1. Reactions of benzothietes **1** and amines **2** in the molar ratio 1:4 and 1:1 [a].

	R	R′	1:4 Product	1:4 Yield [%]	1:1 Products	1:1 Yield [%]	M.p. [°C] [b]
a	H	C_6H_5	**3a**	66	[c]		
b	H	*o*-$CH_3C_6H_4$	**3b**	46	**3b**	11	[d]
					7b	trace	
					9b	31	171
c	H	*m*-$CH_3C_6H_4$	**3c**	65	**3c**	17	[d]
					7c	17	179
					9c	26	65
d	H	*p*-$CH_3C_6H_4$	**3d**	58	**3d**	20	[d]
					7d	21	173
					9d	trace	
e	H	*p*-$CH_3OC_6H_4$	**3e**	70	**3e**	20	[d]
					7e	20	203
					9e	25	211
f	H	$C_6H_5CH_2$	**3f**	45	[c]		
g	CO_2CH_3	C_6H_5	**3g**	32	[c]		

[a] All products were characterized ^{1}H- and ^{13}C-NMR spectroscopically. [b] From petroleum ether 60–90. [c] Not tested. [d] Liquid (see text).

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1 (R=H), 63559-01-3; **1** (R=CO_2CH_3), 58150-62-2; **3a**, 88841-60-5; **3b**, 88841-61-6; **3c**, 88841-62-7; **3d**, 88841-63-8; **3e**, 88841-64-9; **3f**, 88841-65-0; **3g**, 88841-66-1; **7b**, 88841-67-2; **7c**, 88841-68-3; **7d**, 88841-69-4; **7e**, 88841-70-7; **9b**, 88841-71-8; **9c**, 88841-72-9; **9d**, 88841-73-0; **9e**, 53563-22-7; $PhNH_2$, 62-53-3; CH_3–O–$C_6H_4NH_2$, 95-53-4; CH_3-*m*-$C_6H_4NH_2$, 108-44-1; CH_3-*p*-$C_6H_4NH_2$, 106-49-0; CH_3-*p*-$C_6H_4NH_2$, 104-94-9; $PhCH_2NH_2$, 100-46-9.

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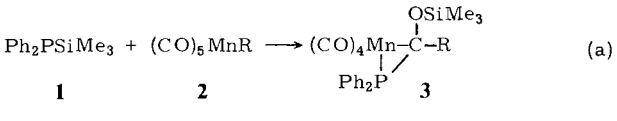
Reactions of Diphenyl(trimethylsilyl)phosphane with Alkyl(pentacarbonyl)manganese; Synthesis of the Ylide Complexes $(CO)_4Mn\overline{Cr(OSiMe_3)}\overline{PPh_2}$ and a New Driving Force for CO Insertion**

By *George D. Vaughn, K. Alex Krein,* and *John A. Gladysz**

Since insertion of CO into an alkyl-metal bond is a key step in many catalytic processes[1], considerable interest has been shown in devising means of kinetically and/or thermodynamically promoting this reaction[2–5]. Recently, it has been demonstrated that Lewis acids[2–4] and ligands which contain Lewis acid sites[5] effect the rapid conversion of alkyl(carbonyl)metal compounds into substituted acylmetal derivatives. We report here that the ligand **1**[4] and alkyl(carbonyl)manganese compounds **2** react to give novel ylide complexes **3** [eq. (a)][5]. In this transformation, an additional driving force—silicon-oxygen bond formation—favors the reaction.



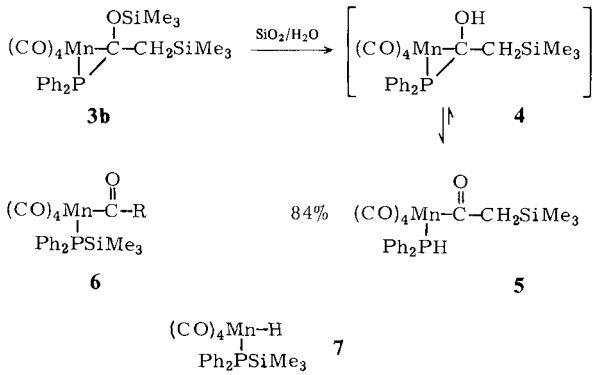
$$Ph_2PSiMe_3 + (CO)_5MnR \longrightarrow (CO)_4Mn(OSiMe_3)(PPh_2)C(R) \quad (a)$$

1 **2** **3**

a, R = Me; **b**, R = CH_2SiMe_3; **c**, R = Ph; **d**, R = 2-Naphthyl

Reaction of **1** with **2a** (molar ratio 1:1.1) in CH_2Cl_2 gave over the course of 12 h complex **3a** in 75% yield (Table 1)[6]. Ylide complexes **3b–d** were prepared in benzene (**3b**: 25°C, 52% yield; **3c** and **3d**, reflux, 67 and 42% yields, respectively) (Table 1)[6].

The following results provide information about the mechanism of complex formation. 1) The rate of disappearance of **2a** was virtually unaffected when triphenylphosphane was substituted for **1**. 2) When **1** and PPh_3 in excess were allowed to compete for **2a**, ca. six times more **1** than PPh_3 was consumed. 3) **1** and the benzoyl complex $(CO)_5MnCOPh$ reacted cleanly to afford **3c** (63% isolated) at a rate ca. four times faster than the reaction of **1** and **2c**. 4) Passage of **3b** through wet silica gel gave the acyclic acyl complex **5**[6] in 84% yield. Presumably **5** is formed via the hydroxy-ylide complex **4**, which, because the O–H bond is weaker than the O–Si bond (103 kcal/mol vs. 106–127 kcal/mol[7]), is thermodynamically unstable with respect to **5**. On the basis of these points, we suggest that the reaction of **1** and **2** to form the ylide complexes **3** proceeds via the substituted acyl complex **6**, which is in turn generated by attack of **1** at the coordinatively unsaturated acyl complex $(CO)_4MnCOR$[8].



3b $\xrightarrow{SiO_2/H_2O}$ **4**

6

84% **5**

7

Remarks relevant to possible extensions of the reaction shown in eq. (a) are as follows: 1) Complex **3a** is inert towards CO (20–25 bar) in CD_3CN or benzene. 2) **1** reacts with the hydride $(CO)_5MnH$ in hexane to afford the complex *cis*-**7** in 76% yield[6]. Hexane solutions of **7** are inert towards CO (ca. 23 bar, 25°C, 3 d). In more polar solvents decomposition occurs. — Equation (a) provides a convenient and distinctly new method[5] for the synthesis of a variety of potentially useful ylide complexes. Extensions to other transition metals can be expected.

Table 1. Spectroscopic characterization of ylide complexes **3**. Coupling constants *J* in Hz.

Compound	IR [cm^{-1}] (ν(C≡O)) [a]	^{1}H-NMR (δ values) [b]	^{13}C-NMR [c, d] CO	^{13}C-NMR [c, d] Other C	^{31}P{^{1}H}-NMR [e]
3a	2054 ms, 1980 s, 1962 vs, 1943 vs	2.14 (d, J_{HP} = 8.4, 3H), 0.14 (s, 9H) [f]	226.5 (s), 221.1 (d, J = 12.6) [d], 219.3 (d, J = 20.5), 216.9 (d, J = 15.6) [f]	68.7 (d, J = 10.2, MnC) [d], 32.2 (s, CCH_3), 1.8 (s, SiC) [f]	7.91 [f]
3b	2053 m, 2048 ms, 1978 m, 1974 ms, 1962 s, 1956 s, 1941 vs	2.02 (dd, J_{HH} = 15.2, J_{HP} = 16.5, 1H), 1.79 (dd, J_{HH} = 15.2, J_{HP} = 1.1, 1H), 0.07 (s, 9H), 0.03 (s, 9H)	224.9 (s), 220.0 (br s), 218.9 (d, J = 16.6), 216.8 (d, J = 16.6)	73.6 (d, J = 37.0, MnC), 36.2 (s, CH_2), 1.4 (s, SiC), 0.2 (s, SiC)	11.7
3c	2057 ms, 1983 s, 1966 vs, 1945 vs	−0.13 (s, 9H)	225.0 (s), 219.5 (d, J = 12.9), 217.8 (d, J = 18.0), 214.8 (d, J = 17.8)	76.9 (d, J = 25.4, MnC), 0.5 (s, SiC)	5.93
3d	2057 ms, 1983 s, 1967 vs, 1945 vs	−0.15 (s, 9H)	224.9 (s), 219.5 (d, J = 10.3), 217.7 (d, J = 17.9), 214.9 (d, J = 15.5)	76.4 (d, J = 25.5, MnC), 0.6 (s, SiC)	7.37

[a] In hexane. [b] 300 MHz in CD_2Cl_2, RT, standard $CHDCl_2$ (5.32). [c] 75 MHz in CD_2Cl_2, −20°C, standard CD_2Cl_2 (53.8). [d] All couplings are to phosphorus. [e] 121 MHz in CD_2Cl_2, RT, standard external H_3PO_4. [f] In CD_3CN, standard Me_4Si.

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CAS Registry numbers:
1, 17154-34-6; **2a**, 13601-24-6; **2b**, 29992-26-5; **2c**, 13985-77-8; **2d**, 88916-68-1; **2** (R=COPh), 15612-92-7; **2** (R=H), 16972-33-1; **3a**, 88932-93-8; **3b**, 88916-69-2; **3c**, 88916-70-5; **3d**, 88916-71-6; **5**, 88916-72-7; **7**, 88916-73-8; CO, 630-08-0.

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[4] G. W. Luther III, G. Beyerle, *Inorg. Syn. 17* (1977) 186.

[5] See, e.g., N. Bresciani, M. Calligaris, P. Delise, G. Nardin, L. Randaccio, *J. Am. Chem. Soc. 96* (1974) 5642; H. H. Karsch, H.-F. Klein, H. Schmidbaur, *Angew. Chem. 87* (1975) 630; *Angew. Chem. Int. Ed. Engl. 14* (1975) 637; S. Al-Jibori, C. Crocker, W. S. McDonald, B. L. Shaw, *J. Chem. Soc. Dalton Trans. 1981*, 1572; H. H. Karsch, *Angew. Chem. 94* (1982) 923; *Angew. Chem. Int. Ed. Engl. 21* (1982) 921; H. Werner, J. Gotzig, *Organometallics 2* (1983) 547; E. Lindner, K. A. Starz, H. J. Eberle, W. Hiller, *Chem. Ber. 116* (1983) 1209; V. C. Gibson, P. D. Grebenik, M. L. H. Green, *J. Chem. Soc. Chem. Commun. 1983*, 1101.

[6] Complexes **3a–d** exhibited M^+ and/or $M^+ - CO$ peaks in the 15 eV mass spectra. Satisfactory elemental analyses were obtained: **3a**: C, H; **3c**, **3d**: C, H, Mn, P, Si. Other new compounds were characterized identically.

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Synthesis and Structure of $[Ph_4As][AuS_9]$, a Cyclic Nonasulfidoaurate(I)**

By *Gerolf Marbach* and *Joachim Strähle**

Very little is known about gold sulfides and thioaurates. Au_2S crystallizes in the cuprite structure[1]; the structure of Au_2S_3[2], which hitherto could only be obtained in the amorphous state, is still unknown. References to thioaurates are to be found in older publications[3], according to which gold sulfides dissolve in aqueous sulfide solution with formation of thioaurates. In a systematic study of gold-sulfur compounds we have also attempted the synthesis of thioaurates and to elucidate their structure. Besides other thio- and polysulfidoaurates we were able to isolate the novel, ring-shaped anion $AuS_9^{\ominus}$ with tetraphenylarsonium as counterion.

$[Ph_4As][AuS_9]$ **1** is formed as main product in the form of bright yellow crystalline platelets on reaction of $K[Au(SCN)_2]$ with tetraphenylarsonium polysulfide in absolute ethanol[4]. The nonasulfidoaurate **1** is stable towards air and light. It dissolves in dimethyl sulfoxide to give a red solution; in contrast, it is insoluble in other organic solvents and water. On treatment with acids it undergoes decomposition with formation of Au_2S.

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The IR spectrum of **1** shows, aside from the known bands for the cation, the weak bands of the Au–S stretching vibration at 325 cm^{-1}; the S–S vibrations cannot be assigned unequivocally, since the bands arising from them are masked by those of the cation.

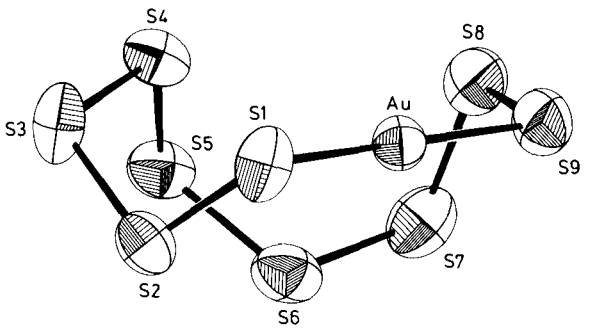

Fig. 1. Structure of the nonasulfidoaurate(I) ion $AuS_9^{\ominus}$. Selected bond lengths [pm] and angles [°]: Au–S1 227.7(1), Au–S9 226.5(3), S–S 203.6(4) to 206.1(5); S–S–S 105.9(2) to 108.2(2), S–Au–S 176.0(1).

As shown by the crystal structure analysis[5] of **1**, the anion consists of a puckered AuS_9 ring (Fig. 1), in which a chain of nine sulfur atoms is bound as chelate ligand to the gold(I) atom. The SAuS angle of 176° is consistent with that expected for linear coordination, which presumably is also decisive for the unusual length of the polysulfide ligand chain. According to model considerations, shorter sulfur chains give rise to less favorable bond angles at the S atoms. In $AuS_9^{\ominus}$ the SSS angles reach the normal value of ca. 107.2°; the S–S bond lengths are on average 204.5 pm. The Au–S distances, with an average value of 227.1 pm, correspond to covalent single bonds. Interactions between the Au atom and the oppositely situated S atoms in the ring can be ruled out, since the distances are too large. Furthermore, there are no short Au–Au contacts like those otherwise frequently observed in Au^I compounds.

The shape of the AuS_9 ring is essentially influenced by the stretched S–Au–S groups. The part of the ring most removed from the Au atom is reminiscent of an "*endo* conformation". In the case of sulfur chains attached as chelate ligands to other transition metals, the smaller bond angle at the central atom leads, in each case, to shorter chains with three, four, five, or six S-atoms. Some typical examples are $[C_5(CH_3)_5]_2TiS_3$[6], $(C_5H_5)_2TiS_5$[7], $[Ni(S_4)_2]^{2\ominus}$[8], $[(S_4)_2MoS]^{2\ominus}$[9], $[Pt(S_5)_3]^{2\ominus}$[10], and $[Hg(S_6)_2]^{2\ominus}$[11].

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CAS Registry numbers:
1, 88867-22-5; $K[Au(SCN)_2]$, 40791-29-5; $[Ph_4As]_2S_6$, 88867-23-6.

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[4] Procedure: A solution of $K[Au(SCN)_2]$ (540 mg, 1.45 mmol) in EtOH (20 mL) is added dropwise to 60 mL of a 0.025 M solution of Ph_4AsS_x (ratio $Ph_4As:S = 2:6$) in anhydrous EtOH). A red-brown, flocculent precipitate is immediately formed. After a few hours, yellow crystals of **1** precipitate out. These are filtered off together with the previously formed precipitate and, after washing with anhydrous EtOH, are dried in vacuo.

[5] The compound **1** crystallizes in the triclinic system, space group $P\bar{1}$, $a=1117.3(5)$, $b=1244.4(4)$, $c=1309.8(2)$ pm, $\alpha=110.19(2)$, $\beta=100.68(3)$, $\gamma=110.69(3)°$, $Z=2$; $R=0.051$ for 1748 independent reflections (ENRAF-NONIUS, CAD4, $Mo_{K\alpha}$). Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD 50641, the names of the authors, and the journal citation.

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[7] H. Köpf, B. Block, M. Schmidt, *Chem. Ber. 101* (1968) 272.

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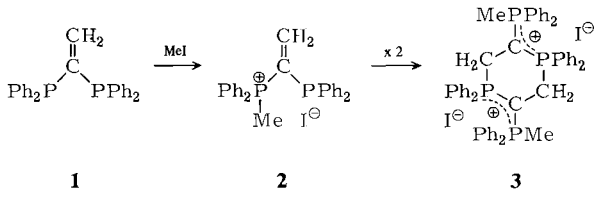
Unexpected Secondary Reaction of the Simple CH_3I-Quaternization of Vinylidenebis(diphenylphosphane)**

By *Hubert Schmidbaur**, *Rudolf Herr*, and *Jürgen Riede*

Vinylidenebis(diphenylphosphane) **1** is the prototype of geminal bis(phosphino)olefins. Its NMR data[1a] and the crystal structure investigation[2,3] have essentially elucidated the conformation and structure, but its reaction behavior (with exception of the chalcogenization[1a,b] has not yet been reported in the literature. Some of the reactions of **1** proceed in an unexpected manner. Thus, we found that even formation of the simple phosphonium salt with alkyl halide leads to a secondary reaction, which, as the first "ylide formation without base", is a remarkable curiosity[4].

Reaction of **1** with methyl iodide (excess) in tetrahydrofuran for 30 min at 20 °C affords the monoquaternary compound **2**, m.p. 128 °C, in more than 75% yield; **2** could be readily characterized by its NMR spectra and by elemental analysis[5]. When solutions of this primary product in methanol are allowed to stand for a few hours at 20 °C, crystals of a novel compound separate out; this, surprisingly, was identified as the head-to-tail [3+3]-cycloaddition product **3** (yield 60%, m.p. 255 °C (decomp.), correct elemental analysis). The ^{31}P-NMR spectrum, in particular, revealed that the two P atoms in each half of the dimeric molecule have become chemically almost equivalent, thus giving grounds for the formulation of **3** as a double semiylide quaternary salt. The spectrum can be simulated as an AA'BB' spin system $\delta(A)=20.17$, $\delta(B)=22.70$; $J(AA')=-5.0$, $J(AB)=39.9$, $J(AB')=23.9$, $J(BB')=11.9$ Hz. In the ^{13}C-NMR spectrum of **3**, the signals of the ylidic C-atoms appear as a doublet of doublets at $\delta=-3.02$ ($J(P_AC)=110.35$, $J(P_BC)=113.28$ Hz)[5].

The FD mass spectrum of **3** shows the line of the dication at m/z 411, as well as the line of the monocation (to which an iodide is still attached) at m/z 949. An analogous behavior has been observed with other 1,3-diquaternary



1 **2** **3**

salts[6]. Correspondingly, the electrical conductivity in CH_3NO_2 also indicates only partial dissociation of **3**: $\Lambda_M=6.45\ \Omega^{-1}\ cm^2$ at 20 °C.

The X-ray structure analysis of **3**[7] shows that the six-membered ring, apparently formed by double intermolecular nucleophilic attack of two non-quaternary P atoms at the terminal C-atoms of the olefinic double bond, has a centrosymmetric chair conformation (Fig. 1). The C=C bond[3] in **1**, which is only 132.7(6) pm long[3], has become the C–C bond in **3**, with a length of 151.3(13) pm. With a P1–C1–P2 valence angle of 125.8 °, the sum of the angles at the bridge C-atom between the phosphorus atoms is 359.7 °, and C1 thus lies in the P1, P2, C2 plane. This arrangement is typical for semiylide quaternary salts $[R_3P{\cdots}CR{\cdots}PR_3]^{\oplus}X^{\ominus}$ with sp^2-hybridized C-atoms.

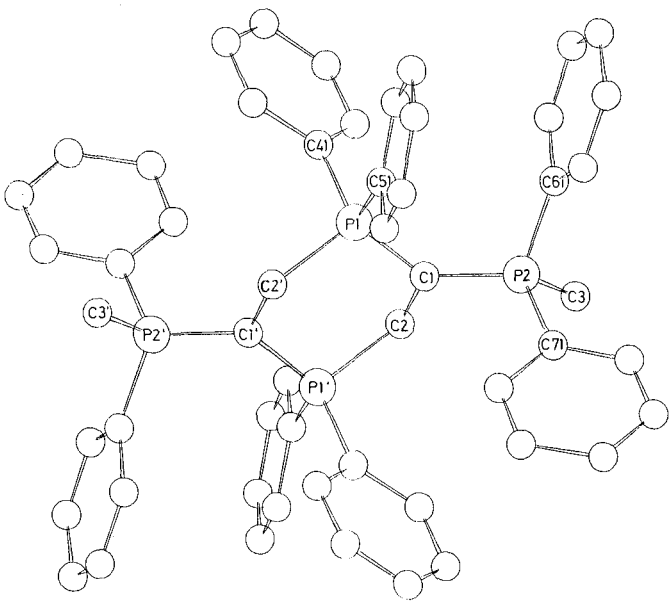


Fig. 1. Structure of the dication in the crystal of the compound **3**. Selected bond lengths [pm] and angles [°]: P1–C1 171.0(8), P2–C1 173.1(8), C1–C2 151.3(13), P2–C3 178.8(11), P1–C2' 182.0(8), P1–C41 178.9(8), P1–C51 178.9(10), P2–C61 180.6(9), P2–C71 179.8)9); P1–C1–P2 125.8(5), P1–C1–C2 116.8(6), P2–C1–C2 117.1(6), C1–P1–C2' 108.3(4), P1–C2'–C1' 113.8(6), C1–P2–C3 109.1(4).

The short P1–C1 and P2–C1 distances of 171.0 and 173.1 pm, respectively, also point to ylidic double bond character (the comparative distances in **1** are 182.9(4) and 183.8(4) pm). The small difference between P1–C1 and P2–C1 in **3** shows that the valence balance in the sense of the formulated mesomeric system is almost complete. The concomitant gain in energy may be regarded as one of the driving forces for the surprising dimerization of **2** to **3** with double ylidization.

The iodide ions in the crystal of **3** have no direct contacts with preferred positions at the dications. Methanol

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molecules present in the crystal are slightly disordered, but likewise without cation or anion contacts. The dimerization found with **2** also occurs with other counterions ($Br^{\ominus}$, $SO_3F^{\ominus}$) and in other solvents (CH_2Cl_2). On rapid methylation of **1** with an excess of FSO_3CH_3, a bis(phosphonium) salt with even stronger activated C=C double bonding is formed. Further, in a wide sense, related cases of the reaction of phosphanes with activated C=C bonds have already been reported in the literature[4,8].

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[1] a) I. J. Colquhoun, W. McFarlane, *J. Chem. Soc. Dalton Trans. 1982*, 1915. b) The *dioxide* (m.p. 204°C) and the *disulfide* (m.p. 184°C) are formed on reaction of 1 with NO and elemental sulfur, respectively. The *diselenide* has already been described [1a].

[2] H. Schmidbaur, *Abstr. Int. Conf. Phosphorus Chem., Nice 5. 9. 1983*, No. 15; *Phosphorus and Sulfur 18* (1983) 167.

[3] H. Schmidbaur, R. Herr, J. Riede, *Chem. Ber. 117* (1984), in press.

[4] Cf. H. J. Bestmann, R. Zimmermann in *Houben-Weyl Methoden der Organischen Chemie, 4th edit., Vol. E1*, p. 616ff., Thieme, Stuttgart 1982.

[5] **2**: ^{1}H-NMR ($CDCl_3$): $\delta(CH_3)=2.1$ (d, 3H, $^2J(PH)=15.0$ Hz), $\delta(CH_2)=5.43$ to 6.50 (ABXY, 2H), $\delta(C_6H_5)=6.64$ to 7.50 (m, 20H); ^{31}P-NMR: $\delta(PPh_2)=-6.12$ (d), $\delta(PPh_2Me)=11.07$ (d, $^2J(PP)=47.3$ Hz).—**3**: ^{1}H-NMR ($CDCl_3$): $\delta(CH_3)=2.02$ (d, 6H, $^2J(PH)=11.0$ Hz), $\delta(CH_2)=4.0$ to 4.63 (m, 4H, [^{31}P] gives singlet signals), $\delta(C_6H_5)=7.3$ to 8.03 (m, 40H); ^{13}C-NMR: $\delta(CH_2)=25.40$ to 28.97 (m), $\delta(CH_3)=13.43$ (dd, $^1J(PC)=57.62$, $^3J(PC)=4.8$ Hz), $\delta(C_6H_5)=120.8$ to 133.65 (m).

[6] H. Schmidbaur, T. Costa, B. Milewski-Mahrla, *Chem. Ber. 114* (1981) 1428.

[7] Colorless, monoclinic crystals from methanol, $a=1354.9(4)$, $b=1961.0(5)$, $c=1160.2(3)$ pm, $\beta=116.7(2)°$, $V=2752\times10^6$ pm^3, space group $P2_1/c$, $Z=2$, $\rho_{calc}=1.38$ g cm^{-3}. $Mo_{K\alpha}$ radiation, graphite collimator, ω-scan (1.1 to 29.3° min^{-1}, $2\theta_{max}\leq48°$, linear absorption coefficient 13.1 cm^{-1}). From 4319 collected reflections, 3335 remained after Lorentz and polarization corrections (77.2%, $I>1.96\sigma(I)$). Heavy atoms according to the Patterson method, all atoms other than H atoms anisotropically refined with full matrix, H-atoms partly found, partly calculated according to ideal geometry (279 variables, 3311 reflections), $R_1=6.4$, $R_2=7.3$%. The CH_3OH molecule is ill-defined and disordered. Further details of the crystal structure investigations are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2 on quoting the depository number CSD 50689, the names of the authors, and the journal citation.

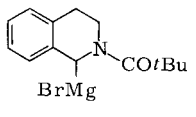
[8] H. Hoffmann, *Chem. Ber. 94* (1961) 1331; S. Trippett, *Chem. Commun. 1966*, 468.

Diastereoselective Hydroxyalkylation of the 1-Position of 2-Pivaloyl-1,2,3,4-tetrahydroisoquinoline via Magnesium Derivatives

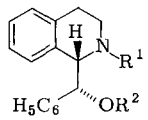
By *Dieter Seebach** and *Max A. Syfrig*

Amide-type derivatives of 1,2,3,4-tetrahydroisoquinolines can be lithiated, and hence alkylated, in the 1-position[1–4]. Whereas an overall enantioselective process could be developed[3], the products of hydroxyalkylation obtained with aldehydes have been reported to be formed with little or no diastereoselectivity[2,4]. We have now discovered[5] that addition of magnesium dibromide ether to solutions of the lithiated 2-pivaloyl-1,2,3,4-tetrahydroisoquinoline in tetrahydrofuran (THF) generates a highly diastereoselective reagent **1**[6].

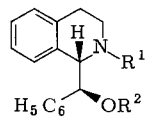
Thus, addition of benzaldehyde to the solution of the magnesium derivative **1**[6] at −78°C leads to isolation of the *u*-isomer of **2a** (m.p. 160°C) in 83% yield. *l*-**2a** could not be detected by ^{1}H- or ^{13}C-NMR spectroscopy. Furthermore, refluxing a solution of *u*-**2a** in methanol/concentrated hydrochloric acid for 8 h produces the ester *u*-**2b** (b.p. 150°C/0.005 torr). The diastereomeric ester *l*-**2b** (m. p. 76–78°C) is formed by refluxing a solution of *u*-**2a** in trifluoroacetic acid/trifluoroacetic anhydride for 2 h. Both reactions are totally selective as indicated by ^{1}H-NMR spectroscopy and give the esters **2b** in ca. 90% yield[7]. Reductive cleavage of the esters *u*-**2b** and *l*-**2b** with $LiAlH_4$ (6 h reflux) in THF furnishes (ca. 65%) the amino alcohols *u*-**2c** (m. p. 73–75°C) and *l*-**2c** (m. p. 102–105°C), respectively. In contrast, a ca. 2:1-mixture of the amide *u*-**2a** and the ester *l*-**2b** is isolated from the reaction of benzaldehyde with the corresponding lithium derivative of **1**. The configurations *u* and *l*[8] were assigned from the NMR spectra of the four *u*/*l*-diastereomeric pairs of **2a–2d**. Notably, in the *l*-isomers of **2a** and **2c** with intramolecular hydrogen bonds the NMR signals of H-8 show a dramatic upfield shift (up to 1 ppm)[9].



1

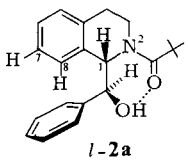


u-**2**

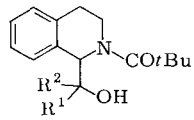


l-**2**

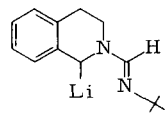
a: R^1 = COtBu, R^2 = H; **b**: R^1 = H, R^2 = COtBu; **c**: R^1 = R^2 = H; **d**: R^1 = R^2 = COtBu



l-**2a**



3



4

The adducts **3a–3d** with other aldehydes were also formed completely selectively (NMR analysis), and even with acetophenone one diastereomer **3e** was produced in 96% *ds* in 90% yield (see Table 1). The configurations of the compounds **3** were assigned by analogy to those of the benzaldehyde adducts **2**.

Table 1. Products **3** from the magnesium derivative **1** and aldehydes, and a ketone. % *ds* indicates the content of the major diastereomer in the crude product; >97% *ds* means that only one diastereomer could be detected by NMR. The values in parentheses are those obtained with **1**, Li instead of MgBr. All yields are >70%; we assume that the *u*-isomer is formed in excess, except in the case of **3e**, which has *l*-configuration according to the ^{1}H-NMR signal of H-8.

3	R^1	R^2	% *ds*	M.p. [°C]
a	H	C_2H_5	>97 (75)	129
b	H	$C_6H_5CH_2$	>97	165
c	H	$C_6H_5CH=CH$	>97	182
d [a]	H	3,4-(methylenedioxy)phenyl	>97	168
e	CH_3	C_6H_5	96 (70)	131

[a] Adduct of **1** and piperonal.

Addition of magnesium bromide to solutions of the lithiated formamidine **4**[2], formed from 1,2,3,4-tetrahydroisoquinoline and *tert*-butylamine, before addition of benzaldehyde, also changes the *u*/*l*-ratio of product **2**

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(R^1=CH=N*t*Bu), R^2=H) from 1:1[2] to 6:1[10]. The results described here demonstrate once again the decisive influence of the metal upon the reactivity and selectivity of even so-called polar organometallic or "carbanion" derivatives.

Access to *both* diastereomers of products of type **2** and **3** is not only interesting in itself, but should provide selective routes to isoquinoline alkaloids with α-hydroxylated side chains in the 1-position[11].

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[10] The chiral formamidine from tetrahydroisoquinoline and 2-phenyl-2-(trimethylsiloxy)-1-(trimethylsiloxymethyl)ethylamine [3] is converted into a 5:1-mixture of *u*- and *l*-**2c** through the magnesium derivative.—Whereas the lithium derivative of the formamidine of piperidine and *t*-butylamine gives a 3:2-mixture of the *l*- and *u*-benzaldehyde adducts (A. I. Meyers, personal communication), a *l*/*u*-ratio of 1:2 is found with the magnesium derivative.
[11] Examples: ushinsunine, guatterine, ophiocarpine, bicuculline, corlumine etc.; see G. Grethe: *"Isoquinolines", Part 1* of: *The Chemistry of Heterocyclic Compounds, Vol. 38*, Wiley, New York 1981; T. Kametani: *The Chemistry of Isoquinoline Alkaloids*, Hirokawa-Elsevier, Tokyo-Amsterdam 1969.

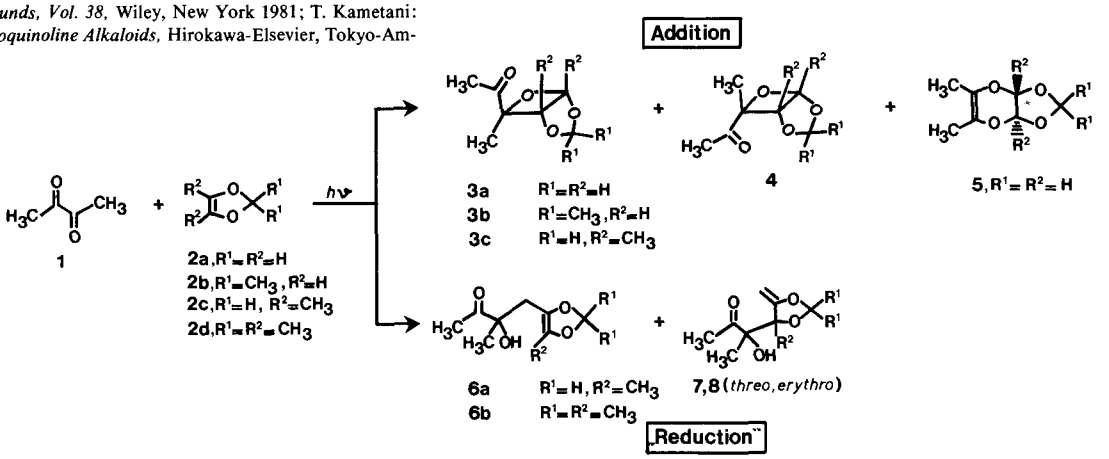
Photoreaction of Biacetyl and 1,3-Dioxole Derivatives: Modification of the Mechanism of the Photoreaction of Carbonyl Compounds with Electron-Rich Olefins**

By *Jochen Mattay**, *Joachim Gersdorf, Hans Leismann,* and *Steen Steenken*

The photoreaction of biacetyl **1** with alkenes usually yields oxetanes and "ene-type" adducts[1]; sometimes enol ("reduction") products formally derived from abstraction of a hydrogen atom from the olefin by the diketone (this corresponds to the first step of the photoreduction)[2]. Generally, exciplexes having some charge transfer (CT) character and diradicals are proposed as intermediates[1,2]. According to *Weller*[3], both locally excited states ($A^*D \leftrightarrow AD^*$) and the CT-configuration ($A^{\ominus}D^{\oplus}$) contribute to the exciplex state formed by excitation of electron donor (D) and acceptor (A) molecules. Stronger electron-donor olefins than those used previously are the substituted 1,3-dioxoles **2**, which have recently become easily accessible[4]. Irradiation of **1** and **2** should lead to formation of exciplexes with more CT-character (contact ion pair according to *Weller*[3]) and also include the possibility of ionic photodissociation in polar solvents[5]. We report here an investigation of the substrate and solvent dependence of the photoreaction and ESR studies under in situ photolysis conditions; the results provide some insight into the effect of charge transfer on the selectivity of this photoreaction.

Preparative irradiation (λ = 400–500 nm) of 1:1 mixtures of **1** and **2** (concentration: 0.1–0.5 mol/L) in cyclohexane or benzene results in formation of the cycloadducts **3–5** and the reduction products **6–8** in 50–70% isolated yields. The product ratio depends strongly on the structure and electron donor abilities of **2**:

1. Only dioxoles containing allylic H atoms (**2c**, **d**) form reduction products;



2. A decrease in oxidation potential ($E^{ox}_{1/2}$) results in increased formation of reduction products, for example $\Phi_{reduction}/\Phi_{addition}$ = 0.07/0.08 (0.22/<0.02) for **1** + **2c** (**2d**);
3. 1,4-Addition is only observed in the reaction of **2a** with **1**; thereby the dihydrodioxin **5** is formed (**3a** : **4a** : **5** = 1.2 : 1 : 1.1 in benzene).

It is noteworthy that photoreactions under S_1- and T_1-conditions yield the same products in the same ratio; neither varying the concentration of **2** (0.05–500 mmol/L, see luminescence quenching rate constants (Fig. 1)) nor sensitizating **1** by addition of benzophenone had any effect on the result[6].

Figure 1 illustrates that charge transfer is important in the luminescence quenching of **1**[6]. However, plots of $\lg k_q/E^{ox}_{1/2}$ with slopes ca. 1/3 of that expected for full elec-

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[**] The authors thanks Prof. *H.-D. Scharf* for stimulating and helpful discussions.

tron transfer ($-17\ V^{-1}$)[7] and the almost complete absence of solvent effects clearly demonstrate that a contact ion pair ($\mathbf{1}^{\ominus\odot}\,\mathbf{2}^{\oplus\odot}$) cannot be formed in this initial step. In order to check the possibility of full electron transfer, ESR experiments were performed under in situ photolysis conditions[8]. In contrast to investigations by *Schaap* et al.[9] of the photooxygenation of dioxenes sensitized by 9,10-dicyanoanthracene electron transfer processes and measurements of transient absorptions in the benzophenone-dioxene system by *Peters* et al.[10], we were able to simultaneously observe both the radical anion $\mathbf{1}^{\ominus\odot}$ and the radical cations $\mathbf{2d}^{\oplus\odot}$ and $\mathbf{2f}^{\oplus\odot}$ during photoreactions of **1** with **2d** and **2f**, respectively, in acetonitrile (Scheme 1). Similar results were obtained in the reaction of **1** with **2b**[11]. These findings strongly support dissociation into free radical ions as an additional reaction path in the photoreactions of **1** and **2**.

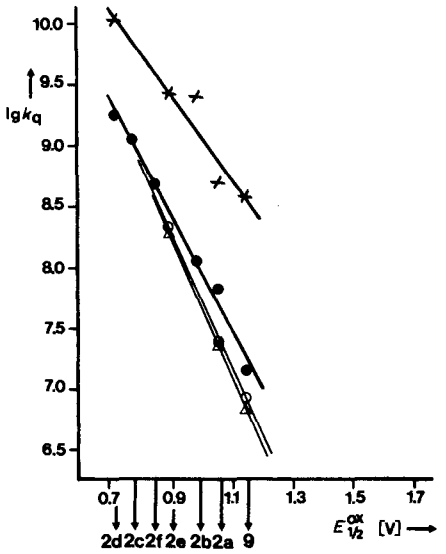
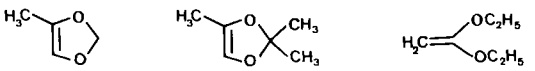
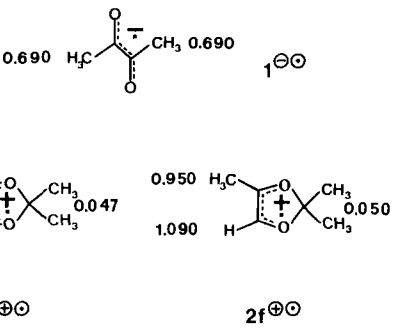


Fig. 1. Rate constants ($\lg k_q$) for the quenching of biacetyl luminescence as a function of the oxidation potential ($E^{ox}_{1/2}$) of the quenchers. (Fluorescence (F) in benzene ×; phosphorescence (P) in benzene ●; in acetonitrile ○, in cyclohexane △). Oxidation potentials (versus SCE) were measured by cyclic voltammetry (Pt working electrode) in acetonitrile; c (quencher) = 1 mM, c ($LiClO_4$) = 0.1 M. The k_q values were calculated using τ_F (benzene) = 9.15 ns and τ_p (benzene) = 284 ± 14, τ_p (cyclohexane) = 180 ± 12, τ_p (acetonitrile) = 358 ± 10 μs, see [6].



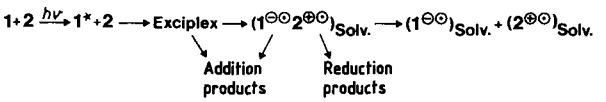
2e **2f** **9**

Recently, we reported[12] the dependence of product quantum yields Φ on solvent polarity in the photoreactions of **1** and **2d** (*Masuhara*'s method[5]). Φ decreases when dissociation into free radical ions becomes exothermic (in solvents with dielectric constant $\varepsilon > 5$). Similar solvent dependences on Φ were observed in all other systems **1** + **2** (Φ decreases by a factor of ca. 2—2.5 when ε is increased from 2 to 37.5). These results together with the ESR studies strongly support the involvement of ionic photodissociation as a competitive reaction path. Moreover, since we are now able to differentiate between an initial step leading to a less polar intermediate ("exciplex"[1]) and a consecutive path yielding radical ions, we propose the mechanism



Scheme 1. ESR coupling constants [mT] of the radical ions $\mathbf{1}^{\ominus\odot}$, $\mathbf{2a}^{\oplus\odot}$, and $\mathbf{2f}^{\oplus\odot}$ in acetonitrile at 0°C.

shown in Scheme 2, an extension of the "exciplex-diradical mechanism" of the Paterno-Büchi reaction[1].



Scheme 2.

Particularly in reactions of strong donors with strong acceptors, H-abstraction seems to proceed via successive transfer of an electron and a proton. Preliminary results with unsymmetrical enol ethers which yield oxetanes of extremely high regioselectivity also indicate participation of polar intermediates in the addition reaction pathway[13]. Other electron donor-acceptor systems (e.g. diketones, aromatic compounds, and electron-rich olefins) exhibit similar reaction selectivities with increasing CT-character.

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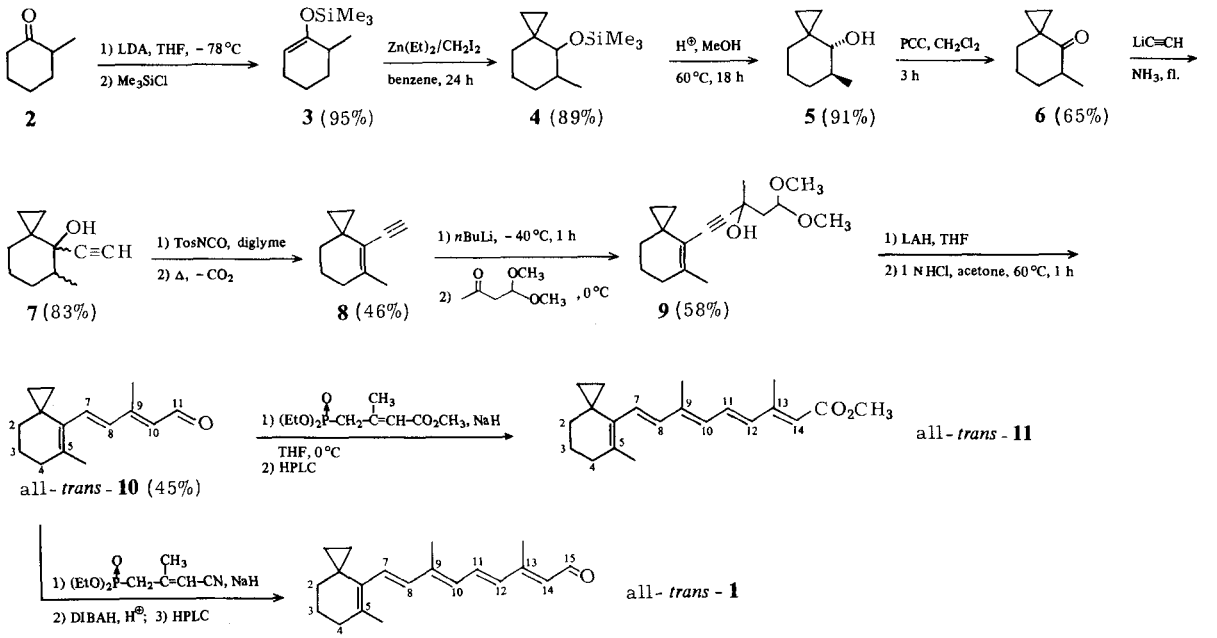
Preparation of Spiroretinal and Related Retinoids**

By *Karin Bartels* and *Henning Hopf**

Retinal ("vitamin A aldehyde") occurs in nature as an essential part of two chromoproteins which fulfill elementary functions in photo-activated processes. Thus in halobacteria light is converted into chemical energy by bacteriorhodopsin, whereas a nerve impulse is triggered via the visual pigment rhodopsin when light falls on the eyes of vertebrates[2]. To study the molecular mechanisms of the two photoreactions, retinals whose substitution pattern is different from that of naturally occurring retinal may be bonded to the apoprotein, and the biochemical properties of the reconstituted, modified rhodopsin probed[2]. In order to be able to clearly distinguish between the steric and electronic effects of a substituent change, the synthesis of vitamin A derivatives („retinoids") is desirable which either deviate in their electronic, but not steric, properties from native vitamin A derivatives, or vice versa.

The spiroaldehyde **1** may belong to the first type of retinoids: Sterically the *gem*-dimethyl groups in the 1-position of the natural product and the cyclopropane ring should differ only slightly from each other; however, the three-membered ring corresponds electronically to a double bond, and hence **1** could be a quasi cross-conjugated polyenal[3].

As the key intermediate for **1** (and other "spiroterpenes"), the enyne **8**, was synthesized first (Scheme 1). For this purpose, the enol ether **3**, obtained from **2** according to the method described by *Murai* et al., was converted into the spiro compound **4**, whose protecting group can readily be removed with methanolic citric acid. Oxidation of the alcohol **5** (trans-arrangement of the methyl and hydroxy groups according to NMR analysis) affords the ketone **6**, which can be ethynylated in good yield to the propargyl alcohol **7** (diastereomeric mixture). Of several reagents for the dehydration **7**→**8**, tosyl isocyanate[6] proved to be the best; convential reagents such as $POCl_3$ and dimethyl sulfoxide gave rise predominantly to products with a cleaved three-membered ring. The chain-lengthening step from **8** to **1** proceeded by means of methods routine in vitamin A chemistry[7]: the "spiro-C_{15}-aldehyde" **10** was obtained as a mixture of the all-*trans*- and 9-*cis*-isomers (2.5 : 1) from the tertiary alcohol **9** via its diastereoselective reduction and subsequent elimination/deblocking. Wittig-Horner olefination of **10** with methyl 4-diethoxyphosphoryl-3-methylcrotonate led to the "spiroretinate" **11** (63%), which according to HPLC (2% ether/cyclohexane) consisted of four isomers: all-*trans*- (84%), 13-*cis*- (23%), 9-*cis* (14%) and 9-*cis*-13-*cis*-**11** (9%)[8]. On the other hand, **10** reacts with 4-diethoxyphosphoryl-3-methylcrotonitrile to form the spiroretinonitrile (63%), which was reduced to a mixture of spiroretinals (41%). From this, all-*trans*-**1** could be isolated by HPLC (relative amount 37%); its structure, as those of the other isomers [13-*cis*- (31%), 9-*cis*- (20%), and 9-*cis*-13-*cis*-**1** (12%)] was determined principally from the high-field NMR spectra (for ^{1}H-NMR data of all-*trans*-**1**, see Scheme 1)[8].



Scheme 1. Abbreviations: LDA = lithium diisopropylamide, THF = tetrahydrofuran, PCC = pyridinium chlorochromate, LAH = lithium tetrahydridoaluminate, DIBAH = diisobutylaluminum hydride. — ^{1}H-NMR of all-*trans*-**1** (400.1 MHz, $CDCl_3$, int. TMS): $\delta = 10.10$ (d, $J_{14,15} = 8.0$ Hz, H-15), 7.11 (pseudo-dd, H-11), 6.37 (d, $J_{11,12} = 15.0$ Hz, H-12), 6.17 (d, $J_{10,11} = 11.5$ Hz, H-10), 6.10 (d, $J_{7,8} = 16.0$ Hz, H-8), 5.97 (d, $J_{14,15} = 8.0$ Hz, H-14), 5.88 (ps-d, $J_{7,8} = 16.0$ Hz, H-7), 2.32 (pseudo-s, 13-CH_3), 2.16 (m, H-4), 1.96 (pseudo-s, 9-CH_3), 1.74 (pseudo-s, 5-CH_3), 1.78—1.70 and 1.48—1.45 (m, H-2, H-3), 0.71 and 0.31 (each pseudo-q, cyclopropyl-H).

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[**] Retinoids, Part 3. The novel compounds **1** and **4**—**11** were characterized by elemental analysis or by high-resolution mass spectroscopy and the usual spectroscopic data. This work was supported by the Fonds der Chemischen Industrie and the Deutsche Forschungsgemeinschaft. — Part 2: [1].

The three-membered ring exhibits a weakly hypsochromic influence on the electronic spectrum: Whereas all-*trans*-retinal absorbs at 388 nm (isopropyl alcohol, $\varepsilon = 42900$), the absorption maximum of all-*trans*-**1** occurs at 378 nm (isopropyl alcohol, $\varepsilon = 41300$). The chemical shift of the polyene protons are only influenced if they lie in the spatial vicinity of the three-membered ring. Thus $\Delta\delta$

($\delta_{\text{all-}trans\text{-retinal}} - \delta_{\text{all-}trans\text{-1}}$) for H-7 is 0.48, but in contrast is only 0.08 for H-8; this effect is also exhibited by H-11 and H-12: $\Delta\delta = 0.04$ and 0.0, respectively.

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BOOK REVIEWS

Lehrbuch der Physikalischen Chemie. By *G. Wedler*. Verlag Chemie, Weinheim 1982. xxii, 914 pp., bound, DM 98.00

The new textbook "Lehrbuch der Physikalischen Chemie" by *G. Wedler* presents a detailed coverage of physical chemistry in the German language. The author has—in his own words—"tried to write a textbook, which, in spite of the limitation of its subject matter to the presentation of the basic principles, is still sufficient to allow application to particular problems".

The preface is "An Introduction to Basic Physicochemical Concepts and Methods". This includes the material which is presented in the first semester as an introduction to physical chemistry or as part of a general chemistry course. Chemical thermodynamics, the kinetic theory of gases, statistical thermodynamics, quantum theory, chemical kinetics and electrochemistry are summarized prior to the main text. This introduction is followed by five main chapters Chemical Thermodynamics, Structure of Matter, Statistical Theory of Matter, Transport Phenomena, Kinetics and a Mathematical Addendum.

The chapter on "Chemical Thermodynamics" (233 pp.) treats chemical equilibra, phase and surface equilibria as well as electromotive forces in detail, alongside with the basic equations of thermodynamics. The chapter entitled the "Structure of Matter" (161 pp.) begins with the quantum mechanical treatment of simple systems, followed by a discussion of the interaction between radiation and atoms and molecules and ends with treatment of chemical bonding. A section is included covering the behavior of material in electric and magnetic fields.

"The Statistical Theory of Matter" (77 pp.) begins with a comparison of the various sorts of statistics and includes statistical thermodynamics and the kinetic theory of gases.

"Transport Phenomena" (42 pp.) deals with the general equation of transport, with diffusion, internal friction, thermal conductivity, electrical conductivity, as well as electrokinetic phenomena.

"Kinetics" (108 pp.) contains sections on experimental methods, formal kinetics, reaction mechanisms, kinetic theory, solution kinetics, the kinetics of heterogeneous reactions as well as catalysis and the kinetics of electrode processes.

The author has included a detailed Introduction in order to demonstrate how the various areas of physical chemistry are interwoven. However, this intention is not always obvious and the book would be no less attractive if the introductory remarks were included in the relevant chapters.

The five main chapters differ greatly in their breadth and depth. The detailed treatment of chemical thermodynamics reflects the importance of this topic. The section "Matter in Electric an Magnetic Fields" inserted into "The Structure of Matter" is written from a very different point of view than the surrounding material. The section "Interactions between Radiation and Molecules" does not include the laser among the basic considerations. This light source is doubtless an important tool in physical chemistry and it might be asked whether it would not have been advisable to include a section entitled "Photophysics and Photochemistry". The inclusion of the laser alongside fluorescence and phosphorescence under "Emissions by Electronically Excited States" might have been more understandable if the term "Stimulated Emissions" had been chosen instead of "Laser".

The chapter on the statistical theory of matter along with its appropriate introduction in Statistical Thermodynamics deserves special mention. The care which the author has devoted to presenting statistics and explaining their relevance to physical chemistry has undoubtedly been worthwhile. It is appropriate that an illustration from this section graces the book's cover.

The chapters entitled "The Structure of Matter" and "The Statistical Theory of Matter" deal with their subjects in a much more advanced and demanding manner than the chapter entitled "Kinetics". The mathematical addendum and the examples of calculations with solutions will undoubtedly be of value to chemistry students.

The Introduction to Electrochemistry at the beginning of this textbook does not correspond to a chapter on electrochemistry, rather the physical chemistry of electrochemistry is dealt with in several sections. A summary could be helpful for study.

This book enriches the available choice of textbooks which are written in German. When compared with translations and, in particular, with textbooks published in English, where language difficulties aggravate problems with the subject matter, this is an advantage which should not be underrated.

The book is clearly and understandably written; the care taken with the detailed derivations will ease the student's task in learning. This detailed physical chemistry textbook is, at least, as much to be recommended as other good textbooks.

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Fragrance Chemistry: The Science of the Sense of Smell. Edited by *E. T. Theimer.* Academic Press, New York 1982. xiii, 635 pp., bound, $ 89.50.

This book sets out to describe the significant classes of fragrance compounds from a chemical point of view. It contains sixteen chapters: *T. V. Getchell, M. L. Getchell,* Physiology of Vertebrate Olfactory Chemoreception, 26 pp.; *J. E. Amoore:* Odor Theory and Odor Classification, 49 pp.; *M. G. J. Beets:* Odor and Stimulant Structure, 46 pp.; *H. Boelens:* Acyclic Monoterpene Alcohols with a 2,6-Dimethyloctane Skeleton, 42 pp.; *P. C. Trass:* Advances in the Chemistry of Some Interesting Cyclic Monoterpene Alcohols, 45 pp.; *V. Herout:* Sesquiterpene Alcohols, 45 pp.; *E. T. Theimer:* Benzene Derived Cyclic Carbinols, 18 pp.; *P. Z. Bedoukian:* Violet Fragrance Compounds, 32 pp.; *H. van den Dool:* Synthesis of Vetiver Oil Components, 32 pp.; *E. P. Demole:* The Fragrance of Jasmine, 48 pp.; *E.-J. Brunke, E. Klein:* Chemistry of Sandalwood Fragrance, 37 pp.; *B. D. Mookherjee, R. A. Wilson:* The Chemistry and Fragrance of Natural Musk Compounds, 61 pp.; *T. F. Wood:* Chemistry of Synthetic Musks I (Non-Benzenoid Musks) and II (Benzenoid Musks), 14 pp. and 34 pp. resp.; *G. Ohloff:* The Fragrance of Ambergris, 40 pp.; and *J. P. Walradt:* Analysis of Fragrance Materials, 42 pp.

The strictly chemical chapters are thus preceded by sections on the physiology of the olfactory system, the mechanism of the sense of smell, and odor-structure correlations in odorous molecules, which, taken together, constitute a fifth of the volume.

Chapter 4 considers the fundamental building blocks of geraniol, nerol, linalool, citronellol, myrcenol and dihydromyrcenol detailing their syntheses and chemical reactions. In the following chapter, the chemistry of menthol, α-terpineol, and borneol receive the prominence they deserve; however the lengthy sections on verbenol, myrtenol, pinocarveol and the boll-weevil pheromones seem out of proportion with their importance to the perfumery industry. The same criticism holds for Chapter 6 where sections on industrially important C15 alcohols such as farnesol, nerolidol, santalol and cedrol rub shoulders with such exotic sesquiterpenes as terrestrol, acorenol and hinesol. Surely, caryophyllene alcohol and acetate, briefly mentioned in the introduction to the chapter, deserve a more detailed treatment.

The editor's own contribution (Chapter 7) covers a curious miscellany—*p-tert*-butylcyclohexyl alcohol, benzyl alcohol, styrallyl alcohol, dimethylbenzylcarbinol and their corresponding acetates, together with 2-phenylethanol. However the comments regarding the different routes to phenylethanol make interesting reading and his exposition on the use of aluminum chloride and Grignard reagents on an industrial scale deserves a wide audience.

Bedoukian's survey of violet odorants rightly emphasizes the importance of the ionones and methylionones in this area, and then briefly touches on irones, damascones, nonadienal and acetylenic esters. In contrast Chapter 9 has only a modest essay on the vetyvenyl acetate of the perfumery industry; it concentrates on α- and β-vetivone, and the history of the structural confusion regarding the latter.

Modern jasmine odorants are described in Chapter 10. The character impact constituents of jasmine oil, *Z*-jasmone, jasmone lactone, and methyl jasmonate, are specified and their syntheses described. Consequently many of the newer synthetic approaches to cyclopentanones are summarized. The chemistry of the sandalwood fragrance follows, in which a good balance between santalols and terpenyl cyclohexanols has been achieved.

The next three chapters cover the various musk odorants. *Mookherjee* and *Wilson*'s contribution contains some interesting unpublished observations on the macrocyclic materials present in natural musk extracts. The synthetic sequences to these materials are subdivided into three groups—intramolecular ring closure, methylation of cyclopentadecanone, and ring expansion and/or contraction, the last including a substantial amount of peripheral material. The monocyclic and polycyclic (indane, tetralin, and isochroman) benzenoid musk odorants and the purely synthetic macrocyclic musks (*e.g.* ethylene brassylate) are covered thoroughly in the other two chapters.

Ohloff, in his chapter on the ambergris odor, covers a dauntingly large number of compounds, but nevertheless demonstrates clearly that the triaxial rule still applies in this area of fragrance chemistry. Finally, *Walradt* summarizes the more recent developments in instrumental analysis and spectroscopy within the context of the perfumery industry.

To sum up, the topics this volume covers, it generally covers well; however, such important fragrance materials as the aliphatic aldehydes, hydroxycitronellal, hexylcinnamic aldehyde, coumarin, heliotropin, and rose oxide receive scarcely a mention.

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Lehrbuch der Lebensmittelchemie. *By H.-D. Belitz* and *W. Grosch.* Springer Verlag, Berlin 1982. xxxviii, 788 pp., bound, DM 124.00.

This textbook covers the most important food ingredients (water; amino acids, peptides, proteins; enzymes; lipids; carbohydrates; flavoring; vitamins and minerals) as well as the most important groups of foodstuffs (milk and dairy products; eggs; meat; fish; whalemeat, crustaceans, shellfish and molluscs; edible fats and oils; grain and grain products; legumes; vegetables and vegetable products; fruit and fruit products; sugar, sugar alcohols and honey; alcoholic beverages; coffee, tea, cocoa; spices, salt

and vinegar) in 23 chapters. Because of their topical importance the subjects of the contamination of food and of food additives have a chapter devoted to them.

The authors present a detailed account of the physical and chemical properties of the important food components, in order to emphasize the relationship between structure and properties at both the level of the ingredient and of the foodstuff. This applies particularly in the case of flavoring and taste. In order to limit the size of the book the authors have concentrated on the *chemistry* of foods, and, where possible, impart information in clearly arranged figures and tables. The large number of well-presented formulae and reaction schemes is also worth mentioning and is in favorable contrast to other—particularly older—textbooks. A far-ranging discussion of the nutritional, technological, texicological and legal aspects of the subject has been deliberately avoided. The information concerning commodities and amounts produced, required by the food chemist, is presented in an elegant, tabular review. The book also contains a range of analytical information which is relevant in judging foodstuffs.

In summary it may be said that this book gives a good review of the modern state of food chemistry. The authors have succeeded in presenting the subject synoptically and precisely. It must not remain unmentioned that important themes, such as cosmetics, commodities in relation to food commerce and tobacco products, which are, nowadays, integrated in to food chemistry, are not treated at all. The clear and comprehensive table of contents and index are worthy of praise. This book is both highly suitable for students of food chemistry, chemistry and related subjects and as a reference work and could well become one of the standard works on the subject within a very short time. However, in view of the high price it is questionable whether it will achieve the circulation it deserves.

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Reactive Intermediates. Volume 3. Edited by *R. A. Abramovitch.* Plenum Press, New York 1983. xiv, 630 pp., bound, $ 59.50.

Three volumes of this open-ended series have now appeared, in quick succession (Volume 1: 1980; Volume 2: 1982; Volume 3: 1983). The contributions presented are intended to provide the interested reader with in-depth reviews of the present state of relatively new fields of the chemistry of reactive intermediates. The aim is to give the work as a whole—but not necessarily the individual chapters—an interdisciplinary character, dealing with themes from widely separated fields, encompassing atmospheric, biological, and industrial chemistry, as well as inorganic and organic chemistry. Hence, this series has a somewhat different objective from another series of the same name (editors *M. Jones Jr.* and *R. A. Moss,* at present two volumes), which is devoted more to the current knowledge of the conventional intermediates of organic chemistry (carbanions, carbocations, carbon radicals, carbenes and nitrenes).

The present volume, comprising seven chapters, begins with a contribution on the chemistry of selenium and tellurium atoms (*J. R. Marquart, R. L. Belford,* and *L. C. Graciano,* 60 p.). Alongside their generation (excited electronic states included) the reactions of these atoms are described, such as recombination, abstraction, insertion into C–H and Si–H bonds, as well as addition to C–C multiple bonds. A wealth of energetic and kinetic data is assembled into tables. The potential importance of these, to the non-specialist exotic-seeming species, not only in intermediate products and energy storage (lasers), is emphasized; the relationship with the chemistry of the lower chalcogens is often accentuated by comparison.

A reaction type which was formally only of theoretical interest, homolytic aromatic substitution by alkyl radicals, is the subject of the second chapter (*M. Tiecco* and *L. Testaferri,* 61 p.). In this field, considerable strides have been made in recent years in the understanding of polar effects on homolytic reactions. This type of reaction also forms the basis of an interesting preparative technique, in particular for the synthesis of certain substituted aromatic heterocyclics. In the following sections *J. W. Wilt* reports on radical reactions of silanes (85 p.) and *W. G. Bentrude* on phosphoranyl radicals (99 p.). Besides the formation of the radicals, their physical characteristics, isomerization behavior, reactions and synthetic potential are treated in detail.

The fifth contribution, by *G. Szeimies,* covers the numerous developments in the second half of the 1970s in the field of strained olefins with bridgehead double bonds (67 p.). Bridged annulenes and compounds with hetero double bonds are deliberately excluded. Emphasis is rather on the syntheses and characterization reactions for individual members of this class of reactive compounds, which is subdivided into three types. Generalizing answers to the interesting questions concerning the structure of strained C–C double bonds rest on a rather small fundament of experimental structural and energetic data. — The reactivity of alkoxyl radicals and their applications in synthesis are dealt with by *P. Brun* and *B. Waegell* (59 p.). After describing the various routes to these short-lived intermediates, particular emphasis is placed on the various applications of their intra- and intermolecular reactions.

The extensive last chapter (*Z. Rappoport,* 188 p.) is devoted to vinyl cations. In contrast to earlier reviews and to a monograph co-authored by the same author that appeared in 1979, in which vinyl cations were discussed primarily in terms of the method of their generation or the nature of the activating group, a welcome attempt has been made here to emphasize the similarities and differences between ions of different structural families and to view the field as a whole.—The volume concludes with an index (13 p.), appropriate in size and detail to the work. An indication of the reactive intermediates treated in previous volumes would have been desirable, however.

All the chapters are compiled by experts, clearly written and so constructed that even a newcomer to the field can easily follow the latest developments. The relevant literature is covered up to 1980/81. Over 1500 original references illustrate, amongst other things, the depth of treatment of the material. Even though the price of the volume may distract the interest of individuals in acquiring it, this collection of comprehensive reviews belongs in every specialized library. The intention of informing the reader about the importance of reactive intermediates outside his specialized field, has also been fully taken into account by the editor, for intermediates with reactive centers on elements so diverse as C, Si, P, O, Se and Te are included.

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Ullmanns Encyklopädie der technischen Chemie. Edited by *E. Bartholomé, E. Biekert, H. Hellmann, H. Ley †, W. M. Weigert †,* and *E. Weise.* Verlag Chemie, Weinheim 1982. 4th Edition,, Volume 22: Stähle bis Textilfärberei. xiv, 716 pp., price DM 545.00.

Like its predecessors Volume 22 of Ullmann, which is now available, contains a large number of entries that are of interest to every chemist. An example of the synoptical and comprehensive form of the presentation, which is understandable and readable in spite of the wealth of detail, is given by the heading "Tenside" (surfactants) (61 pages). Two introductory sections on surface tension phenomena and historical development are followed by a description of the properties of aqueous surfactant solutions and their correlation with constitution. The groups of surfactants are then described, primarily from the point of view of their properties and the processes conventionally used in their manufacture. There follow sections on the analysis, methods of testing, application, and economic aspects of surfactants. The final section under this keyword ("Tenside in der Umwelt") deals with environmental aspects. Incidentally, eight of the 215 literature references come from 1982, an indication of the topicality of the presentation.

The entries in this volume cover the whole spectrum of applied chemistry. For example, from inorganic chemistry alone we have: strontium, tantalum, tellurium and their compounds, nitrogen; from organic chemistry: styrene, terephthalic acid, terpenes; from materials science: steel (164 pages), stoneware; from applications technology: textile printing (69 pages) and textile dyeing (82 pages); from food technology: sweeteners, tea; entries concerning specific problems of applied chemistry: radiation chemistry (33 pages), superconduction (13 pages); from the field of natural raw materials and derived products: starch (44 pates), tar and pitch (36 pages), tall oil, and tobacco and tobacco products (18 pages). In the last mentioned section one learns, for instance, that tobacco plants are often utilized as bioindicators. Somewhat later comes "heavy metals such as lead and cadmium, which are available to the plant from composted rubbish and activated sludge are taken up by the tobacco plant and stored in the leaves." It is certain that addicted smokers will be just as little impressed by this as by the section on the "toxicology of tobacco smoke", where at the close it is stated hopefully "that in future the mortality ratios (smoker/nonsmoker) will turn out better" (because of, inter alia, the changes made to cigarettes in the last 20 years, e.g. reduction of the tar and nicotine contents by half).

The overall impression gained from this volume is that the "Ullmann quality", in terms of content and presentation, is firmly established.

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Liebigs Experimentalvorlesung, Vorlesungsbuch und Kekulés Mitschrift. Edited and commented on by *O. P. Krätz* and *C. Priesner* in collaboration with *O. Kratz, A. Diem,* and *S. von Moisy.* Verlag Chemie, Weinheim 1983. xii, 498 pp., bound, DM 160.00.

It is well known that it was *Justus von Liebig* who initiated the style of modern university chemistry courses with his practice of intimately linking academic teaching with practical instruction in the laboratory. The strand that binds the two main themes of chemical education is the lecture demonstration, and this fact alone is sufficient justification for this volume of Liebig's notes for a demonstration lecture together with a set of student notes derived from it. Furthermore, an insight is given into the knowledge, problems and way of thinking of a leading chemist in the mid-nineteenth century, which is surely not merely of interest to historians of chemistry.

The book of lecture notes which *Liebig* probably had prepared for his son *Georg*—in copybook handwriting with carefully executed drawings of laboratory apparatus—is reproduced in facsimile; the original test is printed alongside and is competently commented upon in many annotations. There is no need for an extensive justification to convince us that such a lecture from the mid-ninteenth century, which has been largely "translated" into present-day chemistry by the editors, constitutes a veritable treasure chest for anyone who wishes to learn more than usual about the first climaxes of classical chemistry. The student's notes on *Liebig*'s lecture were compiled by no less than *August Kekulé.* They are not reproduced here as manuscript copies, but the editors have complemented the printed word with some of *Kekulé*'s original sketches, and have again added some useful, carefully worded comments.

The editors have not seen their task as the simple reproduction of the book of lecture notes and the student's notes; they have created a living picture of *Liebig* and his chemistry in the introductions to the two main portions. The various chapters of both introductions, mainly written by *Otto Krätz,* make gripping reading; the authors command just such a polished style as they rightly attribute to *Liebig,* and with *Liebig* they have a character, who is interesting because he himself inspired interest. Contrary to their own opinion the authors have not failed in their attempt "to produce a sketch of the many faceted *Liebig*", and this, in particular, because they lay the enigmatic personality of this great chemist, with all its contradictions, bare before us. And to boot, we learn a great deal more about *Liebig* himself and the general political and social environment in which he lived—particularly his Bavarian surroundings—and peripherally, but still clearly contoured, about *Liebig*'s son *Georg,* about the Bavarian monarch, *Maximilian II,* about the poet *Paul Heyse,* and not least about *August Kekulé.* The faultless presentation of this book, the excellently chosen photographs and pictures concerning the subject "Liebig" and the often amusing and instructive details, which are to be found in abundance even in the footnotes, do not require any further mention here. It might be added, however, that the authors do not stray into the realms of pure anecdote. Their clear feeling for the times and for the people protects them from that, but their every line vindicates by example the opinion of *Golo Mann* about the writing of history in bloodless, quantitative and sociological terms when he described "the extraordinary entertainment of history".

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Phospholipids as Functional Constituents of Biomembranes**

By Hansjörg Eibl*

This article describes new methods for the synthesis of biologically active phospholipids. The physical properties of such compounds are directly related to their chemical structure, the position of the substituents esterified with glycerol not only influencing the physical properties but also the biological function of the phospholipids. Phase transitions can be induced by temperature changes and—in biological systems—by changes in the surface charge or the degree of protonation. In model studies, the properties of lipid phases differ sufficiently to influence and control biological membrane processes. Alkyl glycerides can modify the properties of biological membranes quickly and reversibly to increase the permeation of active compounds. An important example is the improved transport of cytostatic drugs across the blood-brain barrier. Knowledge about the substrate specificity of enzymes that metabolize phospholipids allows the synthesis of tailored cytotoxic phospholipids which selectively accumulate in malignant tissues. Thus, the interplay of chemical synthesis and investigations of physical structure lays a foundation for the understanding of simple membrane processes on a molecular level, and the experience gained with such model systems can, in turn, be used to influence natural membranes, such as those of the blood-brain barrier or of tumors, in a directed way.

1. Introduction[***]

Biological membranes are complex in structure and function. Their quantitatively dominant constituents are phospholipids and proteins that favor the formation of planar bilayer membranes in an aqueous environment. This tendency to aggregate and to form organized structures derives from the architecture and amphoteric character of the phospholipid molecules, which exhibit lipid-soluble, lipophilic or non-polar regions and water-soluble, hydrophilic or polar regions on the same molecule.

The nomenclature of phospholipids[1] is based on a proposal by *Hirschmann*[2]. Naturally occurring phospholipids contain glycerol which is esterified in positions 1 and 2 with fatty acids and in position 3 with phosphate. Thus, the systematic designation of phosphatidic acid (PA) is 1,2-diacyl-*sn*-glycero-3-phosphate (where *sn* means 'stereospecific numbering'). The specific and non-random distribution of substituents over the positions 1, 2 and 3 of the glycerol molecule introduces chirality. The respective (*S*)-enantiomer, 2,3-diacyl-*sn*-glycero-1-phosphate, has not been detected in nature.

In typical membrane phospholipids the phosphate group is esterified with an additional alcohol, for instance in phosphatidylcholine (PC), phosphatidylethanolamine[1b] (PE) and phosphatidylglycerol (PG) (Scheme 1). Depending upon the structure of the polar region, these phospholipid molecules are neutral at pH values of about 7 (zwitter-

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[**] Extended version of a lecture delivered on October 29, 1982 in München on the occasion of being presented with the Heinrich Wieland Prize.

[***] Abbreviations: DCC: dicyclohexylcarbodiimide; Boc: *tert*-butoxycarbonyl; 1,2-PP-GPC: 1,2-dipalmitoyl-*sn*-glycero-3-phosphocholine; T_P: phase transition temperature of the pretransition P; T_M: phase transition temperature of the main transition M; $Et_{18}OCH_3$: 1-octadecyl-2-methyl-*rac*-glycero-3-phosphocholine.

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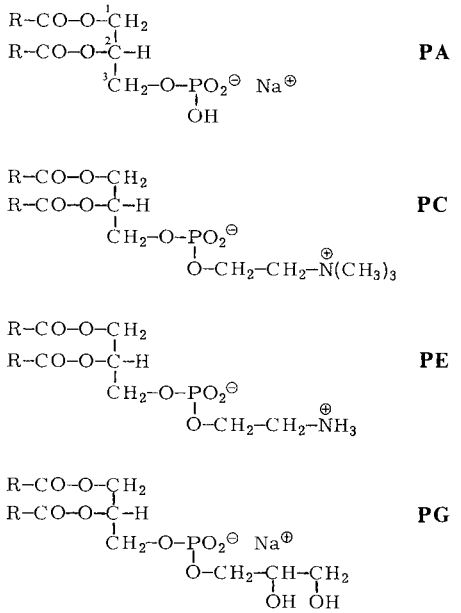
ionic: PC and PE) or exhibit a negative surface charge (PA and PG).



Scheme 1. Typical membrane phospholipids with abbreviations (see text). R represents a long-chain alkyl residue which can contain one or more double bonds. A synthetic analogue of PG is called PP which indicates the lack of a hydroxyl group at C-2 of the glycerol (see Table 5).

In their classic work on the composition of erythrocyte membranes, *Gorter* and *Grendel*[3] were able to show that the phospholipids present in the membrane are sufficient to cover the cell surface with a lipid bilayer. This finding constituted a milestone in biomembrane research and logically became an integral part of all later theories of biological membranes. Surprisingly, the membrane model proposed by *Danielli* and *Dawson*[4] in 1935 has retained its fundamental significance even today: the basic element of biological membranes is the lipid bilayer. The polar regions of the phospholipid molecules are oriented towards the water phase, and the nonpolar parts of the molecules form a hydrophobic phase separating two aqueous regions (Fig. 1). This bilayer structure remained fundamental for many later membrane models such as the 'unit membrane' theory of *Robertson*[5] and in the models of *Finean*[6], of *Singer* and *Nicolson*[7] and of *Lynen*[8]. Only seldom have proteins been proposed as the structural building blocks of biological membranes[9,10].

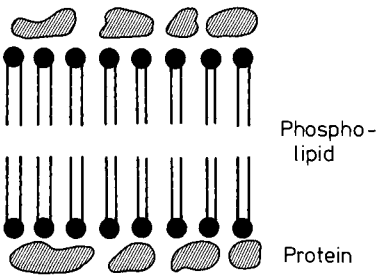


Fig. 1. Membrane model according to *Danielli* and *Dawson* (1935) [4].

Living cells are surrounded by a plasma membrane which defines their extent and insures their integrity by separating the cytoplasm from the surrounding medium. Also, membranes structure the cell interior. Subcellular particles are compartmented by membranes that allow them to operate as separate functional units. For example, the endoplasmic reticulum provides a place for phospholipid[11,12] and protein synthesis[13], and mitochondria are dedicated to the production and storage of energy[10] (ATP-synthesis). It is therefore not surprising that membranes constitute over 90% of a biological cell's dry substance.

The natural border regions of cells and subcellular compartments are membranes which are the main topic of the following discussion. Membranes are composed of a large number of different phospholipid and protein molecules. They form a very complex bilayer matrix and must fulfill multiple functions in close and precise interaction with the environment. The complex structure and the manifold functions normally prevent a detailed study, for example of the interactions between proteins and phospholipids, on a molecular level. Therefore, single membrane processes must be extracted from their natural surroundings and reconstructed in model systems providing a physically and chemically defined lipid environment. Consequently, membrane research involves studies at four levels: 1) synthesis of phospholipids with a well-defined structure and configuration, 2) analysis of the physical properties of phospholipid/water systems, 3) reconstitution experiments, or the reactivation of biological membrane functions in synthetic phospholipid membranes (allowing the study of individual membrane processes), and 4) the selective modification of natural cell membranes.

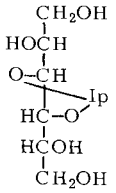
2. Synthesis of Phospholipids

The increasing significance of phospholipids as carriers for drugs with increased bioavailability[14] or as drugs[15] on their own, as well as their importance as membrane model systems[16-18] present a challenge for the synthetic chemist. The growing interest in these chemically variable structures is reflected in the increasing number of publications describing the synthetic or semisynthetic preparation of phospholipids.

The first synthesis of a phospholipid with natural configuration was described by *Rose*[19]. The classical work of *Baer*[20] and of *de Haas* and *van Deenen*[21] followed. More recent techniques have been collected in numerous review articles[22-28].

Hitherto, the usual starting substance for the synthesis of phospholipids has been 1,2-isopropylidene-*sn*-glycerol, whose problematic storage (racemization) and occasionally unsatisfactory optical purity have been criticized[29,30]. We have now developed new routes for the synthesis of phospholipids. The starting material is a stable D-mannitol derivative, 3,4-isopropylidene-D-mannitol **1**, whose synthesis was first described by *Wiggins et al.*[31]. Although stable and easily prepared, this compound was for some reason not often used in lipid work. It is prepared from D-mannitol by reaction with acetone/H_2SO_4. The intermediate, 1,2:3,4:5,6-triisopropylidene-D-mannitol, is con-

verted into 3,4-isopropylidene-D-mannitol **1** by mild hydrolysis with aqueous acetic acid.



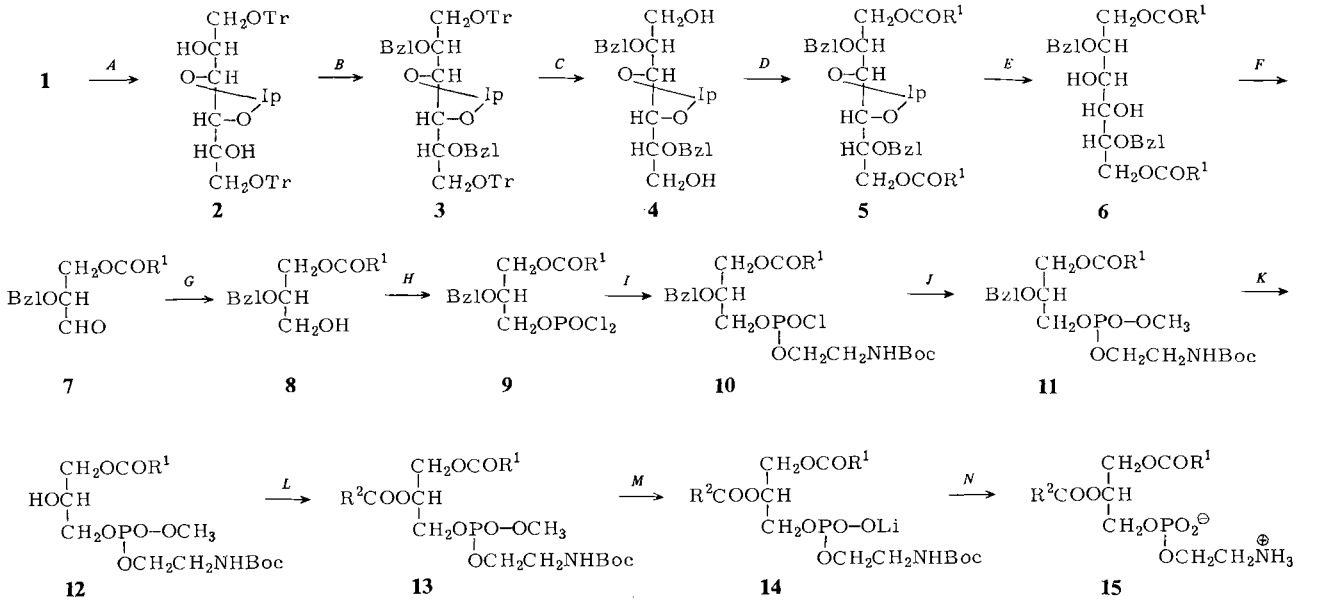
1, Ip = $C(CH_3)_2$

The synthesis of phospholipids starting from 3,4-isopropylidene-D-mannitol is outlined for four different structures of biological significance. The first, 1-palmitoyl-2-oleoyl-*sn*-glycero-3-phosphoethanolamine **15**[28], is an important phospholipid for the induction of ion channels mediated by acetylcholine receptor protein[32,33]. The second, 1-hexadecyl-2-acetyl-*sn*-glycero-3-phosphocholine **21**[34], is a biological mediator[35] frequently called the 'platelet activating factor' (PAF). The third, 1-octadecyl-*sn*-glycero-3-phosphotrimethylammoniohexanol **27**[27], is a phospholipid with an increased phosphorus-nitrogen separation which alters its metabolism and may impart properties that inhibit tumor growth[36]. The fourth, 1,2-dioleoyl-*sn*-glycero-3-phosphoserine **35**[28], has been found to induce the fusion of liposomes[37].

These four model substances illustrate the close link between the chemical structure and biological function of phospholipids. Small variations in structure can lead to dramatic changes in biological activity. For instance, thrombocytes are activated by 1-hexadecyl-2-acetyl-*sn*-glycero-3-phosphocholine **21** in a concentration of 10^{-10} mol/L[35]. The corresponding lyso compound (or 2-deacyl compound) is inactive, but exerts an immunostimulating activity like that of 1-octadecyl-2-methyl-*rac*-glycero-3-phosphocholine (cf. **52**, Table 7)[38–40].

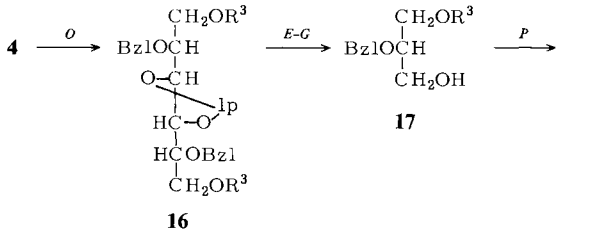
These and other observations have led us to study the relationship between chemical structure and biological activity, and in particular the biologically important interactions between phospholipids and proteins. A prerequisite for such studies is that simple procedures for the preparation and stepwise modification of phospholipid molecules should be available.

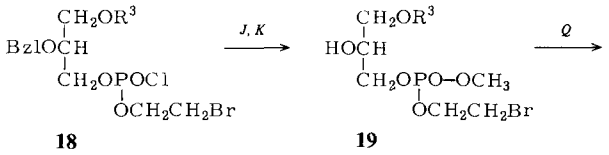
The synthesis of 1-palmitoyl-2-oleoyl-*sn*-glycero-3-phosphoethanolamine **15**[28] is outlined in Scheme 2. Tritylation of 3,4-isopropylidene-D-mannitol **1** with trityl chloride in tetrahydrofuran (THF)/triethylamine (step *A*) furnishes the 1,6-dityrityl derivative **2**, which is then benzylated in positions 2 and 5 to give **3** (step *B*). The trityl groups are then selectively removed from **3** in methanol/2-propanol/H_2SO_4 (step *C*) to give 2,5-dibenzyl-3,4-isopropylidene-D-mannitol **4**. This is esterified in dichloromethane with palmitic acid/dicyclohexylcarbodiimide(DCC)/4-(dimethylamino)pyridine to give 2,5-dibenzyl-1,6-dipalmitoyl-3,4-isopropylidene-D-mannitol **5** (step *D*), in which the palmitoyl group has reached its final position (*sn*-1). Acidic deacetonation of **5** in chloroform/trifluoracetic acid/70% $HClO_4$ affords 2,5-dibenzyl-1,6-dipalmitoyl-D-mannitol **6** (step *E*), the vicinal diol moiety of which in positions 3 and 4 is cleaved with lead tetraacetate in THF (step *F*); the resulting aldehyde **7** is then reduced with $NaBH_4$ (step *G*) to 1-palmitoyl-2-benzyl-*sn*-glycerol **8**. Phosphorylation of **8**—favorably achieved with $POCl_3$ in THF/triethylamine—yields 1-palmitoyl-2-benzyl-*sn*-glycero-3-phosphodichloride **9** (step *H*). Thus, the phosphoester is attached to the *sn*-3 position. All further compounds derived from **9** will therefore have the natural (*R*)-configuration of the phospholipids which are major constituents of all biological membranes. The phosphorylated product **9** is esterified with *N*-*tert*-butoxycarbonylethanolamine to give **10** (step *I*). Subsequent addition of methanol/triethylamine results in formation of **11** (step *J*), the respective phosphotriester. Catalytic hydrogenolysis of **11** in chloroform/methanol

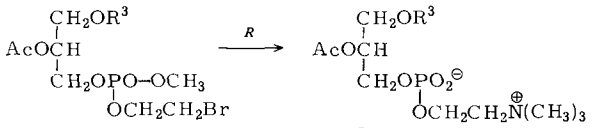


Scheme 2. The synthesis of 1-palmitoyl-2-oleoyl-*sn*-glycero-3-phosphoethanolamine **15**. Boc = $CO-OC(CH_3)_3$; Bzl = $CH_2C_6H_5$; Tr = $C(C_6H_5)_3$; $R^1 = (CH_2)_{14}CH_3$; $R^2 = (CH_2)_7-CH=CH-(CH_2)_7CH_3$. Reaction steps *A* to *N* (see text).

with 10% Pd/C leads to removal of the benzyl group and formation of **12**, which has a free hydroxyl group in the *sn*-2 position (step *K*). Esterification with oleic acid/DCC/4-(dimethylamino)pyridine in dichloromethane affords the 2-oleoyl compound **13** with the oleoyl moiety in the desired 2-position (step *L*). For transformation into the final product, **13** is demethylated in ethyl methyl ketone to **14** (step *M*), from which the *N*-Boc-protecting group is subsequently removed in chloroform/trifluoracetic acid/70% $HClO_4$ (step *N*). The final product **15** is obtained in yields of 40 to 50% based on **1**. Compound **15** is a phosphatidylethanolamine (PE, Scheme 1).



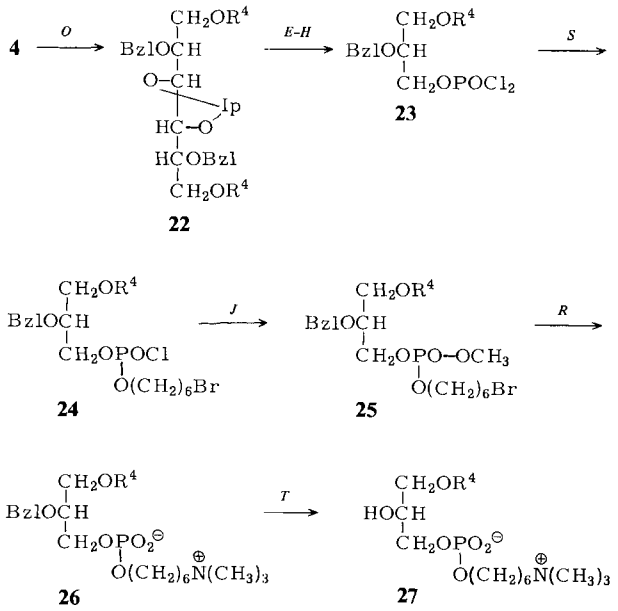




Scheme 3. The synthesis of 1-hexadecyl-2-acetyl-*sn*-glycero-3-phosphocholine **21**. Ac = $COCH_3$; $R^3 = (CH_2)_{15}CH_3$. Reaction steps *O* to *R* (see text).

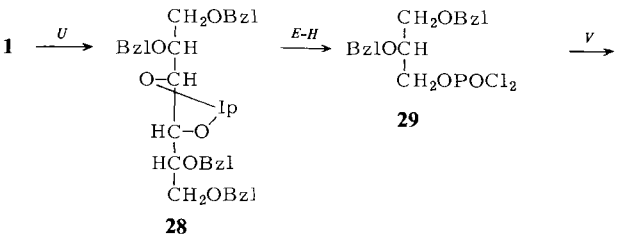
As starting material for the preparation of 1-hexadecyl-2-acetyl-*sn*-glycero-3-phosphocholine **21** (Scheme 3)[34] we used 2,5-dibenzyl-3,4-isopropylidene-D-mannitol **4**. Alkylation of **4** with 1-bromohexadecane in THF/potassium *tert*-butoxide affords 2,5-dibenzyl-3,4-isopropylidene-1,6-dihexadecyl-D-mannitol **16** (step *O*), which is converted into 1-hexadecyl-2-benzyl-*sn*-glycerol **17** in a sequence of reactions analogous to steps *E* to *G* (Scheme 2). The alkyl chain is thus already in the desired position (*sn*-1). Phosphorylation of **17** with bromoethylphosphoric acid dichloride in THF/triethylamine yields the *sn*-3 phosphoric acid derivative **18** (step *P*) having the natural configuration. **18** is converted, in analogy to step *J*, into the respective methyl ester, which is then debenzylated to **19** in analogy to step *K*. Esterification of **19** in dichloromethane with acetic acid/DCC/4-(dimethylamino)pyridine affords **20**, with the acetyl group in the desired *sn*-2 position (step *Q*). The formation of the final product **21** is then possible in one step (step *R*) by amination and demethylation with trimethylamine in chloroform/2-propanol. The yield is about 40% based on **4**.

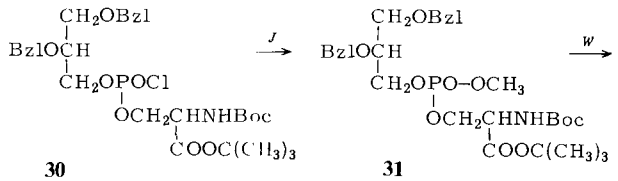
1-Octadecyl-*sn*-glycero-3-phosphotrimethylammoniohexanol **27** (Scheme 4)[27] can also be prepared from compound **4**. In analogy to step *O*, 2,5-dibenzyl-1,6-dioctadec-

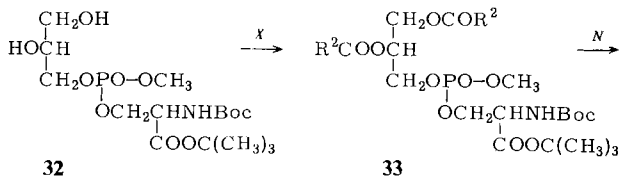


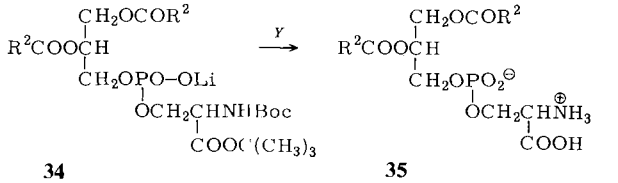
Scheme 4. The synthesis of 1-octadecyl-*sn*-glycero-3-phosphotrimethylammoniohexanol **27**. $R^4 = (CH_2)_{17}CH_3$. Reaction steps *S* and *T* (see text).

yl-3,4-isopropylidene-D-mannitol **22** is obtained using 1-bromooctadecane and is subsequently converted into the phosphoric acid dichloride **23** exactly as shown in steps *E* to *H*. Esterification of **23**, first with bromohexanol result-









Scheme 5. The synthesis of 1,2-dioleoyl-*sn*-glycero-3-phosphoserine **35**. $R^2 = (CH_2)_7–CH=CH–(CH_2)_7CH_3$. Reaction steps *U* to *Y* (see text).

ing in **24** (step *S*) and then with methanol/triethylamine, gives **25** (step *J*). Reaction of **25** according to step *R* provides the phosphocholine analogue **26**. Catalytic hydrogenolysis of **26** in methanol with 10% Pd/C (step *T*) affords **27** in yields of 40% based on **4**.

The synthesis of 1,2-dioleoyl-*sn*-glycero-phosphoserine **35** (Scheme 5)[28] is possible using 3,4-isopropylidene-D-mannitol **1** as starting material. Perbenzylation of **1** in *tert*-butanol/potassium *tert*-butoxide with benzyl chloride (step *U*) gives **28**, which is converted into the phosphoric acid dichloride **29** in analogy to the reaction steps *E* to *H*. **29** is esterified first with *N*-Boc-serine *tert*-butyl ester to **30** (step *V*) and then, in analogy to step *J*, with methanol/ triethylamine to give the phosphoric acid triester **31**. Catalytic debenzylation of **31** with 10% Pd/C in chloroform/methanol under hydrogen (step *W*) yields the phosphotriester **32** which has free hydroxyl groups in positions 1 and 2 of the glycerol molecule. Esterification of **32** with oleic acid/ DCC/4-(dimethylamino)pyridine generates **33** (step *X*). Demethylation in analogy to step *N* with LiBr in ethyl methyl ketone furnishes the protected 1,2-dioleoyl-*sn*-glycero-3-phosphoserine **34**, which is deprotected in one step (*Y*) in chloroform/trifluoroacetic acid/70% $HClO_4$ to give the end product **35**. The yield is about 60% based on **28**.

As shown by examples **15**, **21**, **27** and **35**, tailor-made phospholipids of well-defined structure and configuration can be prepared from simple and stable starting materials in relatively straightforward sequences of reactions. In this way, naturally occurring phospholipids as well as novel structures not found in nature can be synthesized.

The specific, non-random positioning of the fatty acid residues on the glycerol backbone is very important for the physical and biological properties of phospholipids. In natural phospholipids, saturated fatty acids are preferentially found in the *sn*-1 position and unsaturated fatty acids in the *sn*-2 position[41–44]. The physical significance of this finding is discussed in Section 3.

3. Physical Properties of Phospholipid/Water Systems

In water, phospholipids spontaneously assemble into higher molecular aggregates if their concentration surpasses a critical concentration, called the critical micellar concentration (CMC). The type of aggregates formed depends not only on the chemical structure of the lipid but also on physical parameters such as the surface charge, temperature, and the ionic environment. For typical membrane lipids (such as 1-palmitoyl-2-oleoyl-*sn*-glycero-3-phosphocholine) the CMC values are smaller than 10^{-10} mol/L. Therefore, the concentrations of lipid actually dissolved in the water are negligibly small and the phospholipids are true membrane components.

In view of the different kinds of aggregates observed, the question arises whether the most probable conformation of a particular lipid in water can be predicted from its chemical structure according to some general principle. In fact, relatively simple geometric considerations involving the surface area requirement of the molecule allow quite reliable predictions. The data values required for the relative areas occupied by the two parts of the molecule—the polar and nonpolar regions—are obtained from monolayer studies in a Langmuir trough[45], or from X-ray diffraction analysis of phospholipid single crystals[46–48]. Specific conformations are favored if either the polar or nonpolar regions require more area. In this way, the most important types of organized structures formed by phospholipids (micelles, lamellar bilayer structures, vesicles, and hexagonal structures) can be convincingly explained (Fig. 2).

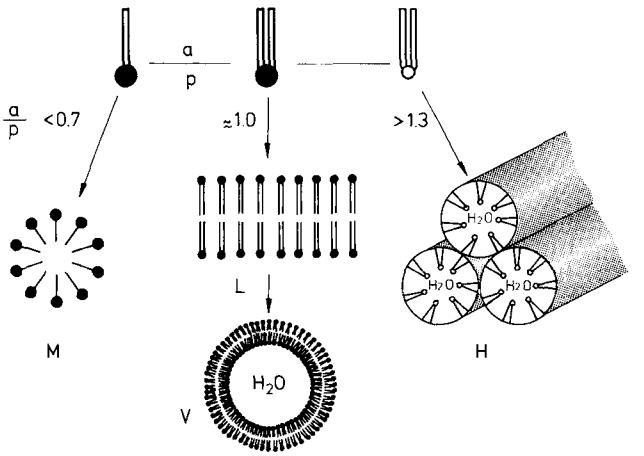


Fig. 2. The organization of phospholipids in water. M: micelle; L: lamellar bilayer; V: vesicle; H: hexagonal structure; a: apolar; p: polar. a/p = ratio of surface requirement of the apolar and the polar region of the molecule.

The decisive parameter is the ratio of the surface requirement of the apolar and the polar regions of the molecule (Table 1). A value near 1 favors the formation of extended lamellar bilayer structures. They can form spheres enclosing water, called vesicles or liposomes. Phosphatidylcholines (lecithins) like **38** are good examples for this behavior (Table 1).

A surface ratio of <0.7 (wedge-shaped molecules with a dominant polar region) leads to the formation of micelles, which differ from vesicles in that the large polar parts of the molecule are oriented towards the water phase and the

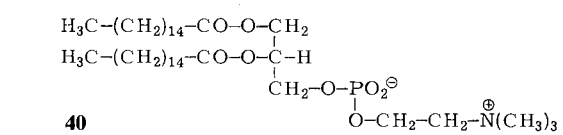
Table 1. The surface area (Å^2/molecule) of phospholipids and of the apolar and polar regions of each molecule. The ratio of the respective surface areas apolar to polar allows predictions about the expected orientation in the presence of water. A ratio of about 1 favors structures such as lamellar bilayers (L); a ratio <1 those of micelles (M) and >1 those of hexagonal structures (H). See also Figure 2. H (L) denotes hexagonal or lamellar, depending on temperature (see also Table 3).

Phospholipids [a]	Surface Area			Ratio apolar to polar	Observed organized structure
	Whole molecule	Regions apolar	polar		
1-Stearoyl-*sn*-G-3-PC **36**	40	20	40	0.50	M
1-Stearoyl-*sn*-G-3-PE **37**	28	20	28	0.71	M (L)
1,2-Distearoyl-*sn*-G-3-PC **38**	44	44	40	1.10	L
1,2-Distearoyl-*sn*-G-3-PE **39**	42	42	28	1.50	H (L)

[a] G-3-PC and G-3-PE denote glycero-3-phosphocholine and glycero-3-phosphoethanolamine, respectively.

fatty acid chains congregate to form an apolar interior. There is no water inside a micelle. Typical micelle formers are monoacylglycerophosphocholines (lysolecithins) like **36**. If the surface ratio is >1.3 (wedge-shaped molecules with larger apolar region), so-called 'inverted micelles' are formed. To avoid confusion with micelles, these structures are now called hexagonal II[*]. Important phospholipids with these properties are the phosphatidylethanolamines (cephalines), as shown in formulas **15**, **37**, and **39**.

Like vesicles, the hexagonal structures enclose an aqueous inner volume. However, in hexagonal structures the aqueous phase is surrounded by a lipid monolayer, whereas in vesicles the aqueous interior is bordered by a bilayer. Lamellar structures can be differentiated from hexagonal arrangements by X-ray analysis.



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1,2-PP-GPC

In the following discussion we will concentrate on the lamellar bilayer phase, because it is the fundamental structure of biological membranes, and reliable detailed information about it is available. Basic experimental data about phospholipid bilayer structures were obtained with 1,2-dipalmitoyl-*sn*-glycero-3-phosphocholine (1,2-PP-GPC, **40**). Starting with the innovative experimental work of *Chapman* et al.[49] this phospholipid has been studied most intensively, so that it is the phospholipid whose phase behavior is best understood today. There are several reasons for this: it is relatively easy to synthesize[28], it has biological significance as the major phospholipid of lung alveolar tissue[50,51], and it exhibits thermotropic phase transitions in the experimentally easily accessible temperature range between 10 and 50 °C. It is therefore reasonable to take 1,2-PP-GPC as an example in discussing the characteristic properties of lamellar phases and to study the influence of structural modifications, both in the polar and nonpolar regions, in relation to the properties of this phospholipid.

According to experimental work with 1,2-PP-GPC in aqueous dispersions this lipid exhibits three calorimetric phase transitions[52-55] when heated from 0 to 50 °C. They are called the subtransition I (phase transition temperature T_{S_I}), the pretransition (phase transition temperature T_P) and the main transition (phase transition temperature T_M). The state below the main transition temperature is called the ordered, crystalline or gel-phase (P_β or P'_β phase[**]) and the state above the main transition is called the fluid or liquid-crystalline phase (L_α phase). Thus, for the heating mode, the main transition is a transition from the ordered to the fluid phase, i.e. from P_β to L_α. The two phases differ in the packing density of the hydrocarbon chains. In the ordered phase, the chains are densely packed with an all-*trans* conformation, whereas the fluid phase represents a more loosely packed matrix (*gauche* conformation)[56]. The state below the pretransition temperature is the L_β phase (above T_P is the P_β phase) and the state below the subtransition I is called the L_α phase (above T_{S_I} is the L_β phase; cf. Fig. 3).

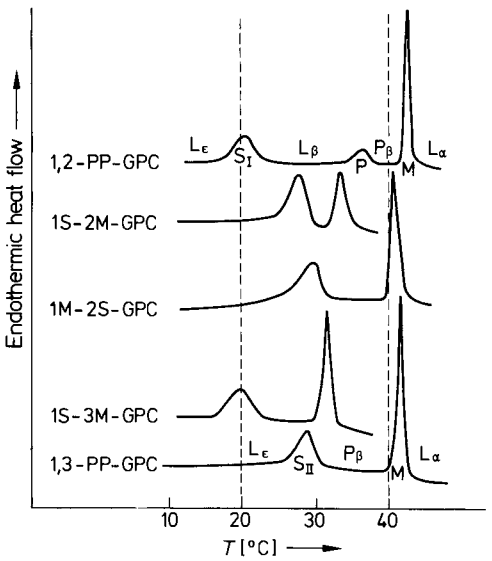


Fig. 3. Calorimetric heating curves of phosphatidylcholines. L_ε, L_β, P_β, L_α: lipid phases; S_I: subtransition I; S_{II}: subtransition II; P: pretransition; M: main transition. Abbreviations for phospholipids see Table 2. A deviation of the heating curve from the base line is observed at a phase transition due to additional heat uptake. The area of the deviation corresponds with the phase transition enthalpy ΔH.

The conformational changes related to the main transition have been directly observed using Laser-Raman spectroscopy[57]. They lead to a considerable contraction of the hydrocarbon chain length (*gauche* conformation) and, accordingly, to a lateral expansion of the bilayer structure. For 1,2-PP-GPC, the following changes were found to accompany the phase change from the ordered to the fluid state (main transition in heating mode): increase in the surface requirement for a single phospholipid molecule from 48 to 70 Å^2[58], shortening of the hydrocarbon chain length by 6 to 7 Å[59], expansion of the bilayer volume by 1 to 2%[59], and onset of rapid lateral diffusion of the lipid molecules due to the decreased van der Waals interaction between the chains above T_M. A lateral diffusion coefficient of 10^{-8} cm^2/s[60,61] was determined for the fluid state, whereas lateral diffusion in the ordered state is immeasurably small.

As demonstrated in reconstitution experiments (Section 4), the main transition is particularly important for biological systems as well as for model studies. It is therefore meaningful to focus attention on the main transition and, because of the amphiphilic nature of the phospholipid molecules, to discuss the influence of the apolar and polar parts of the phospholipid molecule separately. The main transition can react sensitively to small changes in the ionic environment, whereas the subtransition represents a packing change in an already very dense, rigid lipid matrix and thus is isothermally not sensitive to changes in the ionic environment.

[*] Later on, hexagonal is used instead of hexagonal II.

[**] In the work discussed here the tilt angle of the acyl chains to the membrane normal was not estimated. Consequently the primed and unprimed phases were not distinguished. By definition L_ε and L'_ε indicate an orientation of the fatty acid chains parallel to and tilted to the membrane normal, respectively. For simplification, we write L_ε instead of L_ε (L'_ε) etc.

The effects of structural variations in the apolar region were intensively studied with selected phosphatidylcholines. They were of the same molecular weight (Table 2), but differed in the chain lengths of the fatty acid residues[55,62] and also in the respective positions of the fatty acids and phosphocholine along the glycerol backbone[63]. The comparison includes 1,2-dipalmitoyl-*sn*-glycero-3-phosphocholine (1,2-PP-GPC) and its 1,3-isomer, as well as 1,2- and 1,3-isomers of phosphatidylcholines with stearic acid and myristic acid residues in different but defined positions of the glycerol molecule. The lipids can be subdivided into two groups according to the number of thermotropic transitions and the characteristic X-ray diffraction patterns.

1,2-Diacyl-*sn*-glycero-3-phosphocholines with two identical fatty acid chains are found to be exceptional in showing three calorimetric transitions—subtransition I, pretransition, and main transition (Fig. 3) with their respective transition enthalpies. This behavior was described for 1,2-PP-GPC **40** and for 1,2-distearoyl-*sn*-glycero-3-phosphocholine **38** (Table 1) and is most probably also to be expected for the 1,2-dimyristoyl analogue[63]. The corresponding four lipid phases (L_c, L_β, P_β, and L_α) can be characterized by their respective X-ray diffraction lines (Table 2). The number of reflections in the 4 to 10 Å region increases with increasing packing density of the hydrocarbon chains (L_α to L_c) as a result of the increasing crystallinity of the more densely packed L_c-phase.

Table 2. The physical properties of lamellar bilayers of phosphatidylcholines (see also Fig. 3) with increasing temperature, *T*. Phase transitions are indicated at the respective temperature. S_I: subtransition I; S_{II}: subtransition II; P: pretransition; M: main transition; ΔH: phase transition enthalpy; L_c, L_β, P_β, L_α: characteristic phases of the lamellar bilayer arrangement; *d*: distance of the lamellar periodicities which are composed of the thickness of the lamellar bilayer and of the respective water layer between the bilayer lamellas (long distances from 47 to 70 Å); *s*: distance between fatty acid chains and between single phosphatidylcholine molecules which contain two fatty acids per molecule (short distances between 3.72 to 10.00 Å).

Phosphatidylcholines [a]	*T* [°C]	ΔH [kcal/mol]	Phase	*d* [Å]	*s* [Å]
1,2-PP-*sn*-G-3-PC = 1,2-PP-GPC **40**	5		L_c	58.70	10.00, 6.78, 4.40, 4.20, 3.88
	15 (S_I)	4.1			
	20		L_β	63.50	4.20, 4.05
	35 (P)	1.6			
	38		P_β	70.00	4.18
	41 (M)	8.7			
	45		L_α	68.00	4.50
1,3-PP-G-2-PC	5		L_c	57.04	9.63, 6.70, 4.14
	25 (S_{II})	8.0			
	35		P_β	47.10	4.12
	39 (M)	9.4			
	45		L_α	62.16	4.55
IS-2M-*sn*-G-3-PC	4		L_c	67.30	9.55, 4.49, 3.72
	24 (S_{II})	7.9			
	30		P_β	—	4.16
	33 (M)	6.0			
	39		L_α	68.40	4.55
1M-2S-*sn*-G-3-PC	4		L_c	60.40	9.98, 6.75, 4.34, 4.15, 3.86
	26 (S_{II})	6.6			
	31		P_β	69.90	4.15
	42 (M)	8.2			
	46		L_α	63.80	4.55
1S-3M-*sn*-G-2-PC **49**	5		L_c	58.30	9.82, 6.69, 4.33, 4.15, 3.76
	16 (S_{II})	5.9			
	20		P_β	68.30	4.13
	30 (M)	7.1			
	35		L_α	63.40	3.44

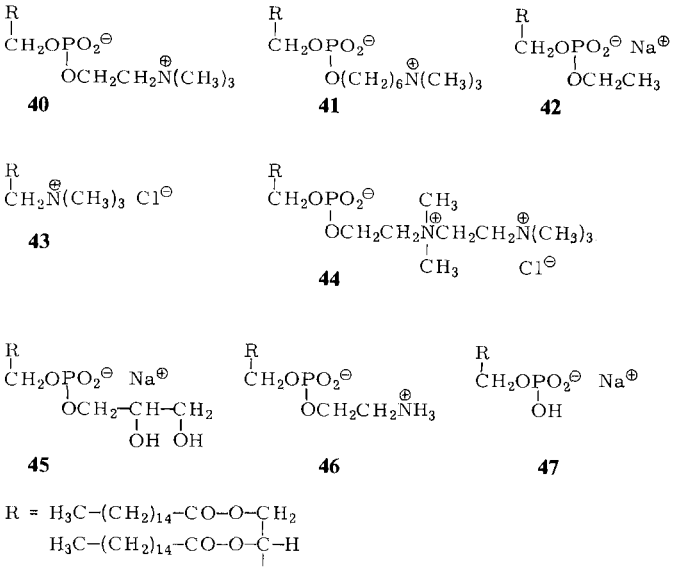
[a] M = myristoyl ($CH_3(CH_2)_{12}CO$), P = palmitoyl ($CH_3(CH_2)_{14}CO$), S = stearoyl ($CH_3(CH_2)_{16}CO$), and GPC = glycerophosphocholine.

All other phosphatidylcholines studied by our group show a different phase behavior. Only two thermotropic transitions are observed, the subtransition II and the main transition. Again, the respective phase transition enthalpies of the lipid phases (L_c, P_β and L_α) and their X-ray diffraction patterns are characteristic for the different lipid phases. The 1,2-diacyl-*sn*-glycero-3-phosphocholines with two different fatty acid residues belong to this class. They are extremely important as naturally occurring biological phospholipids. The same behavior is also observed for 1,3-diacyl-*sn*-2-phosphocholines, independently of whether they contain two identical fatty acid chains or two different fatty acid chains in the same molecule. The most important difference between these two classes of lipids is the absence of the pretransition found for the 1,2-diacyl-*sn*-glycero-3-phosphocholines with two identical fatty acid residues, and most probably the absence of the L_β-phase (for a detailed discussion see [63]).

Biological membranes consist of mixtures of phospholipids which differ in the composition of the fatty acids and also in the surface charge[64]. Therefore structural variations in the polar region of these molecules are studied. *Träuble* and *Eibl*[65] have shown that changes of the surface charge in bilayer membranes can have pronounced effects on the physical properties of the membranes and particularly on the main transition temperature.

The influence of the polar region on the properties of the entire molecule was studied with 1,2-dipalmitoyl-*sn*-glycerol as a constant apolar structural unit. This is advantageous because the discussion in the case of 1,2-PP-GPC can also include the pretransition which is not found for molecules of mixed fatty acid composition. The reference molecule 1,2-PP-GPC **40** was modified as follows: an increase in the phosphorus-nitrogen distance (**41**), removal of the trimethylammonium group (**42**), removal of the phosphate group (**43**), overcompensation of the negatively charged phosphate group by two positive charges (**44**) and substitution of choline by glycerol (**45**). The effect of these extensive structural changes on the physical behavior of phospholipid-water systems at pH 7 is however marginal. The main transition temperatures lie between 40 to 42 °C, and the pretransition occurs at 33 to 36 °C. Thus, the phospholipid bilayer does not respond to these changes in the structure and surface charge of the molecules.

There is, however, another group of lipid molecules for which relatively small changes in structure and/or charge dramatically affect the physical properties. These lipids do not show a pretransition, but are characterized by main transition temperatures far above the main transition temperatures of the aforementioned lipids. For instance, at pH 7 1,2-dipalmitoyl-*sn*-glycero-3-phosphoethanolamine **46** and 1,2-dipalmitoyl-*sn*-glycero-3-phosphate **47** have T_M values near 65 °C; in comparison the corresponding phosphatidylcholine **40** has a T_M of 41 °C.



40 **41** **42**

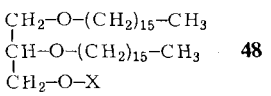
43 **44**

45 **46** **47**

R = $H_3C-(CH_2)_{14}-CO-O-CH_2$
$H_3C-(CH_2)_{14}-CO-O-CH$

In searching for structural analogies between these two groups of molecules which may explain the differences in physical behavior, it appears that the lipids with the higher T_M values (around 65 °C) are protonated. They contain structural and structuring protons within the membrane surface, whereas the lipids with the lower T_M values (near 40 °C) are deprotonated, with the phosphate groups fully charged. Possibly the interplay of forces within the polar region of phospholipid bilayers is decisively influenced by the presence of structural protons within the membrane surface[66,67].

This assumption is easily checked experimentally. If the difference in the degree of protonation, or the degree of dissociation α, is the cause of the drastic differences in the physical properties, similar differences should be found in the transition behavior of one kind of phospholipid molecule at different pH values, above and below the respective pK value. For such studies at extreme pH values from pH 1 to 12 we have prepared phospholipids of type **48** con-



48

taining ether-linked chains instead of the less stable ester bonds, which are subject to hydrolysis. Thus, 1,2-dipalmitoyl-*sn*-glycerol as apolar structural element was replaced by 1,2-dihexadecyl-*sn*-glycerol. The differences in physicochemical behavior between such "ether"- and "ester"-phospholipids have been shown to be small, with the phase transition temperature in the case of the "ether-phosphatidylcholine" increased by about 3 to 4 °C in comparison to the "ester" analogue[68–72].

The phase transition behavior of various "ether-phospholipids" of type **48** was investigated at different pH values, starting at pH 12 and investigating the effect of increasing proton concentration as shown in Figure 4. The deprotonated lipids, 1,2-dihexadecyl-*sn*-glycero-3-phosphocholine, -3-phosphoethanolamine, -3-phosphoglycerol, and -3-phosphate do not differ significantly in their physical properties ($T_M \approx 43$ °C; $T_P \approx 38$ °C). Therefore, the pretransition is not a specific attribute of phosphatidylcholines, but instead is a general property of all phosphocholines with identical chains in the 1 and the 2 position of glycerophosphocholines that are fully dissociated, *i. e.* that do not contain any structural protons within the membrane surface. With increasing proton concentration (lower pH values) the pK values of the polar head-groups become increasingly important[*]. For instance, at pH 11 the amino group of phosphatidylethanolamine binds protons in accordance with its pK value. This drastically changes the properties of the lipid. The pretransition disappears and the main transition is shifted to $T_M > 70$ °C, which is > 30 °C above the main transition temperature of the deprotonated state. The other lipids included in this investigation change their properties with the protonation state in complete analogy to the phosphatidylethanolamine. The pretransition disappears, and the main transition is shifted to higher temperatures. For phosphatidic acid this occurs at pH 9 (pK_2), for phosphatidylglycerol at pH 4 (pK), and for phosphatidylcholine at pH 1 (pK). The physical properties of the "ether-phospholipids" thus depend directly on the degree of protonation; the "ester-phospholipids" behave similarly.

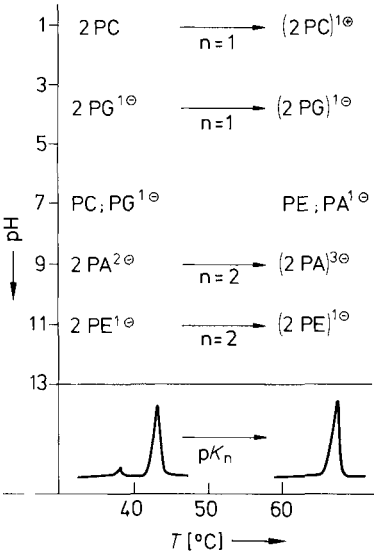


Fig. 4. Influence of the proton concentration on the physical properties of "ether-phospholipids" of type **48**, which were chosen instead of the "ester-phospholipids" because of their better stability. PE, PA, PG and PC stand for 1,2-dihexadecyl-*rac*-glycero-3-phosphoethanolamine, -3-phosphate, -3-phosphoglycerol and -3-phosphocholine. At pH-values > 12 the lipids are all in the deprotonated state and exhibit a pretransition and a main transition. At the pH value of pK_n the main transition temperature is shifted to higher temperatures. A pretransition is no longer detected.

The different pK values of the various phospholipids are therefore of great importance for the function of natural

[*] We have compared the pK values of water soluble glycero-3-phosphate with 1,2-dimyristoyl-*sn*-glycero-3-phosphate [65]. For matrix-bound phosphate residues, the pK values are shifted to higher pH values. For instance glycero-3-phosphate: pK_1 2.0, pK_2 6.0; 1,2-dimyristoyl-*sn*-glycero-3-phosphate: pK_1 4.0, pK_2 9.0. The dissociation of protons from a negatively charged lipid matrix needs more energy than deprotonation of a single molecule.

membrane systems. In the biologically relevant pH region near pH 7, two groups of phospholipids with completely different physical properties coexist: fully dissociated structures and those which are partly protonated. "Ether-phospholipids" with the same apolar region (e.g. 1,2-dihexadecyl-*sn*-glycerol) as the phosphocholine or phosphoglycerol show two transitions with T_M values of about 43 °C and T_P values of about 38 °C, whereas the respective phosphoethanolamines and phosphates exhibit only one transition, namely the main transition at $T_M > 70$ °C (an additional transition to hexagonal also occurs and will be discussed later).

The molecular reason behind the stabilization of the protonated states—higher T_M values due to the more densily packed hydrocarbon chains—is hydrogen bonding between the negatively charged phosphate groups and the positively charged ammonium groups or protonated phosphate residues. Therefore, phosphatidic acid at pH values near 12 (fully dissociated) and near 2 (fully protonated) exhibits a much lower phase transition temperature than in the region between pK_1 and pK_2 (the partially protonated states). Thus, phospholipids with two dissociable protons show a plateau in the phase transition temperature between the pK values. The transition temperatures for the plateau are more than 25 °C higher than the T_M values of the fully dissociated state, and more than 15 °C higher than the T_M value of the fully protonated state (Fig. 5). The extent of the plateau region is determined by the pK values. For "ether-phosphatidylethanolamine" of type **48** it extends from pH 1 to 11, and for the analogous phosphatidic acid from pH 3.5 to 9. For phospholipids with one proton, on the other hand, one expects and finds a maximum in T_M near the pK value; for example, for methyl 1,2-dipalmitoyl-*sn*-glycero-3-phosphate at pH 3.5[73,74].

In addition to the increased T_M values, partly protonated phospholipids like phosphatidylethanolamine may tend to form hexagonal structures (Table 1). For instance, some synthetic phosphatidylethanolamines undergo phase transitions which have been characterized by X-ray analysis as transitions from the lamellar-fluid phase to the hexagonal structure[75]. The dependence of the transition temperatures on the fatty acid chain length differs for the two types of transition. For the transition from lamellar-fluid to hexagonal, T_H decreases with increasing chain length, whereas T_M increases. By contrast, phosphatidic acid cannot form the hexagonal structure at pH 7.

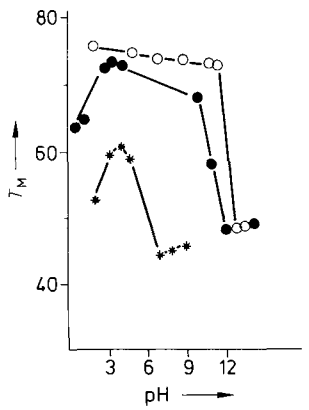


Fig. 5. The pH-dependence of the main transition temperature (T_M) of different phospholipids. ○: 1,2-dihexadecyl-*sn*-glycero-3-phosphoethanolamine (type **48**); ●: 1,2-dihexadecyl-*sn*-glycero-3-phosphate (type **48**); *: 1,2-dipalmitoyl-*sn*-glycero-3-phosphoric acid methyl ester. The extension of the plateau for T_M depends on the difference between pK_1 and pK_n. A phospholipid with only one dissociable proton has a maximum in T_M for the pK value.

In biological systems pH values near 7 are usually maintained, since irreversible damage, such as denaturation of proteins may otherwise result. It is therefore important to search for mechanisms which change the physical properties of lipid-water systems at pH 7 and at constant temperature. A likely 'candidate' is the effect of monovalent and divalent cations on membrane systems.

Monovalent cations may induce the dissociation of protons from the membrane surface[65,74]. A prerequisite for this effect is the presence of partially protonated phospholipids which react sensitively to changes in the concentration of monovalent cations. Then the degree of protonation will change so that T_M for the respective lipid is lowered (deprotonated state). Sensitivity against monovalent cations is thus coupled with the presence of a critical pK value which we generally call the critical pK_n value of a n-proton phospholipid system. Examples are pK_3 of phosphatidylserine (n = 3; pH value near 11), pK_2 for phosphatidic acid (n = 2; pH value near 9) and pK for phosphatidylglycerol (n = 1; pH value near 4) (in the case of phosphatidic acid, pK_1 is not sensitive against monovalent cations and therefore is not a critical pK value, since with increasing concentration of monovalent cations T_M is not lowered—whereas at pK_2, T_M decreases by about 25 °C). In biological membranes at pH 7, natural phospholipids do not show any critical pK values, and thus the influence of monovalent cations on the physical properties is marginal.

The influence of divalent cations, however, is important. At pH 7 and at constant temperatures they can induce phase transitions similar to those which we have described for protons. The sensitivity of the various phospholipids against cations corresponds to their different pK values (Table 3). Phosphatidylcholine and phosphatidylethanolamine are not sensitive. Their characteristic properties, their T_M values, and the particular ability of phosphatidylethanolamine to form hexagonal structures, are unchanged[75,76]. On the other hand, phosphatidylglycerol reacts strongly to the presence of divalent cations such as

Table 3. Influence of cations on the organization of natural phospholipids at pH 7. PC: phosphatidylcholine; PE: phosphatidylethanolamine; PG: phosphatidylglycerol; PA: phosphatidic acid; L: lamellar bilayer; H: hexagonal structure. For a transition from the lamellar to the hexagonal structure the fluid state of the lipid matrix is required. Therefore $T_H > T_M$, since the transition temperature for the transition lamellar fluid to hexagonal is always above the temperature of the transition lamellar gel to lamellar fluid. PE above T_M therefore can arrange in a lamellar or hexagonal structure. The preferred structure depends on the respective temperature. It can be expected that at 37 °C natural PE species prefer the hexagonal arrangement since T_H in most cases lies below the body temperature.

Phospho-lipids	Influence of cations on the structure		
	pH 7	NaCl (1 mol/L)	$CaCl_2$ (0.1 mol/L)
PC	L	L	L
PE	H (L)	H (L)	H (L)
PG	L	L	H (L)
PA	L	L	H (L)

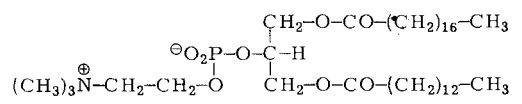
calcium ions, with an increase in T_M by about 24 °C and the ability to undergo the transition to hexagonal structures[76,77]. Phosphatidylglycerol, as calcium salt, behaves very much like phosphatidylethanolamine. In the case of phosphatidic acid T_M is already high, but the binding of calcium additionally allows formation of hexagonal structures at pH 7[76].

Negatively charged phospholipids react stoichiometrically with divalent cations. The binding of magnesium ions leads to an aggregation of vesicles, which retain their integrity and individuality[78]. With the binding of calcium ions aggregation is also observed, but it is followed by fusion[79]. The fusion process results in a profound change in the properties of the system since the individuality of the vesicles is lost. Thus, vesicles of different compositions fuse together, resulting in homogeneous structures[80].

4. Reconstitution Experiments

In reconstitution experiments, biological membrane functions (such as enzyme-catalyzed reactions or membrane transport processes) are extracted from their natural environment, rebuilt in a physically defined system and studied as an individual process. Such experiments can reveal whether specific lipid structures are essential for a particular biological function. The functional constituents of a membrane process are compounds that are inactive in their purified state, but exhibit biological activity when reconstituted in an appropriate functional system. As simple examples we discuss the ion transport through lipid membranes and the biological activity of phospholipid dependent enzymes.

In a pure lipid system, ion transport through a lipid bilayer in the ordered state was first studied by *Boheim* et al.[17]. For these experiments we have synthesized specific mixed-chain phospholipids such as 1-stearoyl-3-myristoyl-*sn*-glycero-2-phosphocholine **49** with T_M near 30 °C (Table 2). These tailor-made phospholipids were found to be ideal film-formers, giving stable planar bilayers both in the fluid and ordered phases, as well as in the transition region. One possible reason for the remarkable properties of these mixed-chain lipids may be the absence of the pretransition.



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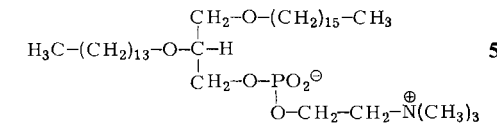

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Cooling curves of planar bilayer membranes are shown in Figure 6. The pure bilayer membrane made from **48** shows a very low conductance, < 1 nA cm^{-2}. However, spontaneous current fluctuations appear at temperatures close to the phase transition. These fluctuations are obviously related with the phase transition of the lipid. Reorientation of lipid molecules in the transition range causes packing defects which lead to the observed conductance changes. The fluctuations are induced by the temperature change through a melting of the chains in the transition region. Other conductance changes in pure lipid systems may be induced by protonation of the phosphate groups and may thus depend on the proton concentration and the availability of a critical pK value[81].

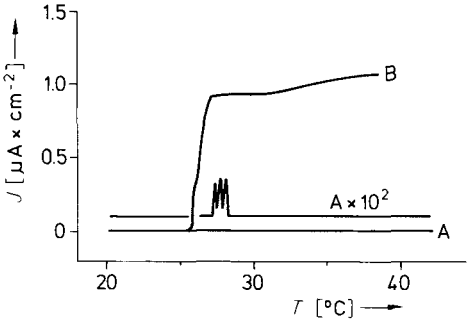


Fig. 6. Changes in conductance of planar lipid bilayers with decreasing temperature (cooling curves). A: current fluctuations of 1-stearoyl-3-myristoyl-*sn*-glycero-2-phosphocholine **49**; A × 10^2: larger scale presentation of A to demonstrate current fluctuations at T_M of the lipid (≈30 °C). B: change in conductance of 1-hexadecyl-2-tetradecyl-*sn*-glycero-3-phosphocholine **50** in the presence of valinomycin and 1 M KCl. In the transition region of the lipid (≈28 °C), a sudden drop of the membrane current is observed.

The influence of the physical state of the lipid matrix on carrier mediated transport processes (Fig. 6) is strong. Conductance values of > 1 μA cm^{-2} are observed in the system 1-hexadecyl-2-tetradecyl-*sn*-glycero-3-phosphocholine **50** in the presence of valinomycin and 1 M KCl if the film is studied in the fluid state at temperatures above T_M (about 28 °C). A sudden decrease in the membrane current is then observed in the transition region: It drops by a factor 10^3 from 1 μA cm^{-2} above T_M to 1 nA cm^{-2} below T_M. Below T_M, the conductance corresponds to that of a film without any carrier. It is reasonable to assume that carrier-induced ion transport depends on the fluid state of the lipid matrix. Like the lateral diffusion of lipid molecules within a monolayer, the rate of ion translocation through the membrane from one monolayer to the other, is undetectably small in the ordered state.

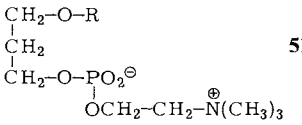
Conductance changes were also found in bilayers made from phospholipid mixtures containing phosphatidylcholine and phosphatidic acid[82]. In the presence of valinomycin and rubidium chloride high conductances are observed. The addition of calcium ions induces a phase separation and produces lipid domains which contain either phosphatidylcholine or phosphatidic acid. Only the phosphatidylcholine domains then contribute to the membrane current, because phosphatidic acid is ordered (below T_M), whereas phosphatidylcholine is in its fluid state (above T_M).

In protein-free lipid systems, carrier-induced ion transport occurs only in the fluid state of the membrane. The reversible phase transition from the ordered into the fluid state and vice versa thus represents a powerful mechanism for regulating membrane currents: a membrane current can flow in the fluid state whereas the current in the or-

dered state is negligibly small. The transition can be induced by temperature changes, but also with calcium ions. In mixtures of lipids containing phosphatidylcholine (insensitive against calcium ions) and phosphatidic acid or other negatively charged phospholipids, the addition of calcium ions may induce phase separation and also increase the main transition temperature T_M.

In lipid-protein systems phase separation can occur via specific interactions between phospholipids and proteins. This is important for the function of D-lactate dehydrogenase from *E. coli*, a phospholipid-dependent enzyme system[83]. The phospholipid composition of the *E. coli* membrane, and probably the properties of the membrane, are imprinted by the dominating role of phosphatidylethanolamines, which represent more than 90% of the membrane lipids. The proportion of negatively charged lipids such as phosphatidylserine and phosphatidylglycerol is small (below 5%). The question arises whether such lipid minorities are of any importance for the biological function.

As shown by *Kovatchev* et al.[84], D-lactate dehydrogenase needs an apolar lipid matrix for its biological function. This was demonstrated with a series of 1-acyl-1,3-propanediolphosphocholines **51** of different chain length. It was possible to measure the activity of the enzyme below and above the CMC of these micelle-forming phosphocholines. As expected, the D-lactate dehydrogenase exerted activity only in the presence of matrix molecules at a higher concentration than the CMC. The activation was clearly a result of the presence of micelles, whereas the monomers



51, R = $CO-(CH_2)_n-CH_3$

Table 4. Critical micelle concentrations (CMC) of 1-acyl-1,3-propanediolphosphocholines **51** in dependence of the chain length of the acyl group. In addition, the concentrations are given which induce a 50% D-lactate dehydrogenase activation (LDH-activation) or 50% hemolysis (of bovine erythrocytes).

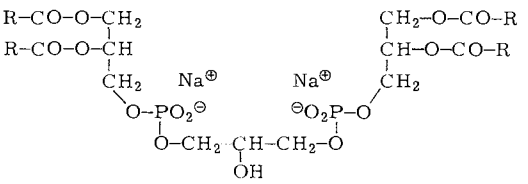
R in **51** [a]	log CMC [mol/L]	log 50% LDH-Act. [mol/L]	log 50% Hemolysis [mol/L]
22:0	−5.05	−5.0	—
20:0	−5.00	−4.50	−4.70
18:0	−4.80	−4.30	−4.70
16:0	−4.70	−4.10	−4.70
14:0	−4.35	−3.70	−4.35
12:0	−3.52	−3.10	−3.60
10:0	−2.46	−2.05	

[a] The acyl groups R in **51** are characterized by the number of double bonds in the fatty acids: 22:0, behenic acid; 20:0, arachic acid; 18:0, stearic acid; 16:0, palmitic acid; 14:0, myristic acid; 12:0, lauric acid; 10:0, decanoic acid.

were virtually inactive. In Table 4, values for the critical concentrations of micelle formation, for the activation of the D-lactate dehydrogenase, and for the hemolysis of bovine erythrocytes are compared for different 1-acyl-1,3-propanediolphosphocholines **51**. These model compounds lack the hydroxyl group in C-2 of glycerol. The close coincidence of the values of the concentration for micelle formation (CMC), for enzyme activation, and for hemolysis is not surprising. These activities all depend on a common property: the surface activity. It induces the formation of micelles and enzyme activation, but also results in a reorientation of the lipid bilayer if the ratio of phospholipid to lysophospholipid falls below 4:1 (hemolysis). Lyso compounds of this type have a free OH group on C-2 of glycerol.

The behavior of D-lactate dehydrogenase in lamellar bilayer structures contributes to an understanding of natural membrane systems. The main phospholipid of the *E. coli* membrane is 1-palmitoyl-2-elaidoyl-*sn*-glycero-3-phosphoethanolamine. Surprisingly, this lipid will not activate the enzyme. Instead, negatively charged phospholipids like phosphatidylserine or phosphatidylglycerol, although only minor constituents of the *E. coli* membranes, do activate the enzyme. This suggests that the native protein in its active state must also be surrounded by negatively charged phospholipids. Thus, the active state of the enzyme in a largely neutral lipid matrix is induced by phase separation, whereas a statistical distribution of the lipids would result in inactivation[84]. Phosphatidylserine and phosphatidylglycerol are therefore functional constituents of *E.-coli* membranes.

Phospholipids are essential for the function of many membrane-bound proteins[85,86]. The requirements for specific lipids, however, are frequently not very stringent. But D-β-hydroxybutyric acid dehydrogenase from bovine cardiac mitochondria[87] needs phosphatidylcholine for enzymatic function[88,89]. In its natural environment, the enzyme is surrounded by phospholipids with highly unsaturated fatty acid residues. The main phospholipids are phosphatidylcholines, phosphatidylethanolamines and bisphosphatidylglycerol (cardiolipin) **52** in a molar ratio of 43:37:20[90,91]. Due to the large number of different fatty acids esterified specifically with the 1- or 2-position of glycerol the diversity of molecular species is large[92].



52, R = $(CH_2)_n-CH_3$

Therefore, it is interesting to inquire what significance the multitude of molecular species, or the presence of bisphosphatidylglycerol **52**, or possible phase transitions from the fluid to the ordered state have for the enzymatic reaction. To answer these questions, we have synthesized many of the various molecular species occurring in the natural membrane, as well as some artificial lipids with the methods described in Section 2. With these structurally and configurationally well-defined molecules we were able to look for some answers to the questions mentioned above.

The results are summarized in Table 5. Although, phosphatidylcholine is essential for the enzymatic activity of D-β-hydroxybutyric acid dehydrogenase, the fine structure of the phosphatidylcholine is of minor importance for the activation process. There is no indication that the presence of highly unsaturated fatty acids in the phospholipids is of

any advantage for the reconstituted systems as long as the lipids are in the fluid state. Almost no activation is found below the main transition temperature; therefore, the fluid state of the membrane is a prerequisite for the activation of the enzyme[93,94].

Table 5. Activation of D-β-hydroxybutyrate dehydrogenase with defined synthetic phospholipid species at 37 °C. Microdispersions of phospholipids were prepared by ultrasonication of PC alone, of PC/PE mixtures (ratio of phosphate 5:4) and of PC/PE/PP mixtures (ratio of phosphate 5:4:1). PC stands for phosphatidylcholines with acyl groups presented in the left column [a]; PE represents phosphatidylethanolamines with the respective acyl groups [a]; PP indicates phosphatidyl-1.3-propanediols with the same acyl groups as in PE (Scheme 1). The numbers give the extent of activation for the enzyme and are based on the activation of the enzyme with the phospholipid extract from mitochondria which is set to 100 per cent. The numbers in parenthesis stand for the effectivity of the phospholipid in the reactivation process (molar ratio of PC to enzyme which results in half-maximal activation). Thus, the smaller the number the better the PC, the PC/PE or the PC/PE/PP mixture. In the case of the natural phospholipid extract of mitochondria an effectivity of 7 was experimentally found. PE or PE/PP mixtures alone do not activate the enzyme.

1,2-Diacyl of PC [a]	PC (alone)	+PE 1-16:0 2-18:1	+PE 1-16:0 2-12:0	+PE/PP 1-16:0 2-18:1	+PE/PP 1-16:0 2-12:0
1-16:0 2-18:1	82 (29)	100 (17)	100 (16)	100 (7)	100 (7)
1-16:0 2-18:2	82 (26)	99 (16)	—	100 (7)	—
1-16:0 2-20:4	85 (27)	100 (13)	—	99 (8)	—
1-22:0 2-18:1	79 (25)	100 (16)	100 (18)	100 (7)	98 (8)
1-16:0 2-14:0	67 (74)	97 (29)	96 (28)	96 (7)	95 (7)
1-16:0 2-12:0	63 (80)	93 (30)	96 (29)	93 (7)	97 (7)

[a] The acyl groups are characterized by the number of carbon atoms and of double bonds, see footnote [a] of Table 4. 20:4, arachidonic acid; 18:2, linoleic acid; 18:1, oleic acid.

Cardiolipin **52** as characteristic phospholipid of the mitochondrial membrane can be substituted by other negatively charged phospholipid molecules without any effect on the kinetic parameters of the enzyme reaction. These experiments allow a clear distinction between phospholipids which are functional components of the enzyme system and others which only provide matrix properties. Phosphatidylcholines are functional constituents of these membranes. However, the matrix properties are also influenced by the phospholipid composition. From the results in Table 5 it is evident that the most favorable matrix properties are obtained in a mixture of phosphatidylcholine/phosphatidylethanolamine/negatively charged phospholipids which closely resembles that found in the natural membrane (except for the fact that the latter contains cardiolipin as the third component).

The large number of different lipid species in the natural membrane does not appear to be important for the enzyme reaction. The only requirements are a fluid state of the lipid matrix and the presence of phosphatidylcholine. Highly unsaturated fatty acids are not essential for the reactivation of this enzyme. In the model system the large number of different lipid species of the natural membrane is replaced by only three different phospholipids which contain only saturated fatty acids in the 1 and the 2 position of the phospholipid molecules. The fluidity of these membranes arises from the use of long-chain fatty acid residues in the 1-position and of short-chain fatty acid residues in the 2-position of the glycerol. For instance, D-β-hydroxybutyric acid dehydrogenase shows optimal activity in a simple lipid matrix composed of 1-palmitoyl-2-lauroyl-*sn*-glycero-3-phosphocholine, -3-phosphoethanolamine and -3-phospho-1,3-propanediol (Table 5, right column, last line). In this mixture phosphatidylcholine is concomitantly a functional constituent as well as a component of the lipid matrix.

Mixtures of phosphatidylethanolamine and phosphatidyl-1,3-propanediol alone (without the phosphatidylcholine) cannot activate the enzyme.

5. Selective Modification of Natural Membranes

The directed modification of natural membranes of cells or subcellular structures is of great medical interest. Methods that allow a selective uptake of drugs by specific organs or organelles have received particular attention. The principles underlying our recent work are illustrated by two specific cases: the problem of the blood-brain barrier and the development of cytotoxic substances that can be detoxified by healthy tissues that lack a specific enzyme.

The blood-brain barrier as a highly selective filter was first described by *Lewandowsky*[95]. It is the reason for the relative resistance of brain metastases against chemical therapy, since an effective concentration of cytostatic substances cannot be reached in the brain. Stimulated by the experiments of *Deuticke*[96] on the influence of short-chain alcohols on the permeability of erythrocyte membranes we have investigated the effect of the physiologically more acceptable alkyl glycerides, such as 1-pentyl-*rac*-glycerol, on the blood-brain barrier.

The method of *Oldendorf*[97] was employed to measure the transport of twelve common cytostatic drugs through the blood-brain barrier. A solution containing a ^{14}C-labeled drug was injected into the right carotid artery of Wistar rats. Following decapitation, the right half of the brain was ashed and its radioactivity determined. The permeability of the blood-brain barrier to the ^{14}C-labeled drugs was measured relative to ^3H_2O as a freely diffusing internal standard. Table 6 summarizes the 'brain uptake index' values determined in this way.

The cytostatics selected differ in their molecular weights (90—1500) and in their oil-water partition coefficients ($\log p$ −3 to +1). According to *Oldendorf*[98], lipophilicity is the decisive parameter determining transport through the blood-brain barrier. According to our results, however, this is correct only for a limited range of molecular weights.

Of the twelve cytostatics tested, only cyclophosphamide (endoxan) and $Et_{18}OCH_3$ can pass the blood-brain barrier in appreciable amounts (about 10%). Cyclophosphamide, however, is not of therapeutic interest because it must be activated in the liver, and the therapeutic value of $Et_{18}OCH_3$ is controversial. Thus, not one of the twelve cytostatics tested meets the requirements for chemotherapy of brain tumors.

Table 6. "Brain Uptake Index" (BUI) values (as ratio of the activities of ^{14}C-labeled drug and free diffusible ^3H_2O as internal standard in the brain and in the injectate times 100) and the oil/water partition coefficients p of cytostatica. The cytostatica are differentiated in three ranges (100 to 500; 500 to 600; 600 to 1500) according to increasing molecular weights (MW). Within each range a subdivision is reached according to increasing lipophilicity. BUI*-values are attained from BUI values by substraction of 3.3 per cent (background of the method). Thus, a BUI value of 3.3 per cent means no uptake. 1-Pentyl-*rac*-glycerol (PeG) was used in physiological concentrations (0.15 M).

Active substance	MW	BUI* value [%] without PeG	BUI* value [%] with PeG	log$p$
5-Fluoruracil	132	0.4	9.7	−2.89
Methotrexate	455	2.0	22.9	−2.44
Cyclophosphamide	262	8.1	50.2	−1.03
Et_{18}-OCH_3 **53** [a]	542	7.4	—	−1.25
Doxorubicin	544	0	—	−1.00
Etoposide	589	0	14.5	−0.62
Daunorubicin	528	0	—	−0.30
Bleomycin	1400	0	2.4	−1.89
Peplomycin	1400	0.9	10.5	−0.74
Vincristine	923	0	—	−0.47
Mitoxantrones	625	0	21.8	+0.13
Vinblastine	909	0	38.3	+0.99

[a] 1-Octadecyl-2-methyl-*rac*-glycero-3-phosphocholine.

A classification of the drugs into three groups is suggested by the results in Table 6. In the range of molecular weights between 90 and 500, the transport properties are determined by the lipophilic properties. The blood-brain barrier acts like a water/oil interface, and the rate of diffusion through the membrane is determined by the oil/water partition coefficient.

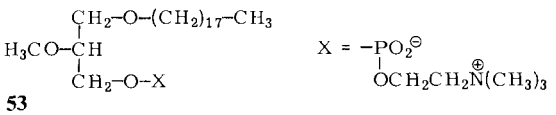
For cytostatics with molecular weights greater than 600, the blood-brain barrier represents a true, impermeable boundary, with the range of molecular weights between 500 and 600 occupying an intermediate position. Such drugs are excluded quite independently of their oil-water partition coefficients. An impressive example is that of vinblastine, which cannot pass the blood-brain barrier[99], in spite of its very favorable partition coefficient (log$p$ +0.99). This experimental result refutes the theory of *Oldendorf*[98], which claims that an oil/water partition coefficient of log$p$ −1 is a sufficient requirement to allow complete delivery of a drug through the blood-brain barrier.

These results suggest that chemotherapy is unlikely to be useful in treating brain tumors because the blood-brain barrier prevents accumulation of an effective concentration of a drug in the brain. However, recently we were able to show that the barrier properties can be favorably influenced by short chain alkylglycerols[100]. Thus, as Table 6 shows, cytostatics with molecular weights below 500 are efficiently transported through the barrier in the presence of 1-pentylglycerol. Indeed, even the transport of drugs with larger molecular weights, up to 1500, is made possible by 1-pentylglycerol. The effect is fully reversible within one minute, which is a major advance over the osmotic shock method of *Rapoport* et al.[101], in which the blood-brain barrier requires several hours to normalize again.

The goal of directing a cytotoxic compound to selected organs or to tumors can thus be achieved by the use of carrier molecules, such as the alkylglycerols in the case of the blood-brain barrier. Since such carriers can only operate above a minimum concentration, they allow transport only in one direction, from the bloodstream into the brain. By dilution in the brain region the concentration falls below the critical minimum value, so that the transported drugs cannot leave the brain area again (cage-effect).

Cytotoxic substances can also be directed to specific organs by exploiting differences in the enzyme pattern. Thus, *Snyder* et al.[102] have observed that tumor cells lack the 1-*O*-alkyl cleavage enzyme found in normal cells. This can be correlated directly with the work of *Westphal, Fischer, Munder* et al.[39,103] on immunostimulating and cytotoxic properties of 1-octadecyl-2-methyl-*rac*-glycero-3-phosphocholine (Et_{18}-OCH_3) **53**. As representative of a possible new class of antitumor agents, Et_{18}-OCH_3 has been intensively studied. It should selectively accumulate in tumor cells and lead there to selective cytolysis. Although the principle of this approach appears convincing, so far it has not been converted into a successful therapy.

To find out why Et_{18}-OCH_3 **53** is also highly toxic for normal cells, we have studied the properties of related compounds as substrates of the 1-*O*-alkyl-cleavage enzyme from rat liver. As a new assay for the enzyme reaction we have measured the formation of water-soluble phosphate[104], thus circumventing the use of ^{14}C-labeled substrates[105]. The results obtained so far are presented in Table 7. It is noteworthy that Et_{18}-OCH_3 is at best a poor sub-



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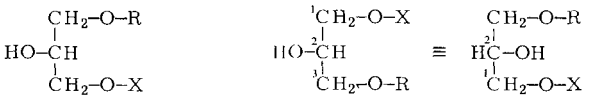

54, R = $(CH_2)_{15}$–CH_3 **55**, R = $(CH_2)_{15}CH_3$

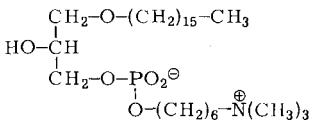

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Table 7. Substrate specificity of the 1-*O*-alkyl cleavage enzyme of rat liver. A specific activity of <0.2 means that probably no reaction occurs (background level of the method). The values are obtained by determination of water soluble phosphate [104] during the enzyme reaction.

Substrates [a]	Specific activity [nmol (mg protein)$^{-1}$ min^{-1}]
1-Hexadecyl-*sn*-G-3-PC **54**	8.0
1-Hexadecyl-*sn*-G-3-P-trimethylammoniohexanol **56**	7.5
3-Hexadecyl-*sn*-G-1-PC **55**	9.0
1-Octadecyl-*sn*-G-3-PC	5.6
1-Octadecyl-2-methyl-*sn*-G-3-PC **53**	<0.2
3-Octadecyl-2-methyl-*sn*-G-1-PC	<0.2
1-Octadecyl-2-methyl-*rac*-G-3-PC	<0.2
1-Methyl-2-octadecyl-*rac*-G-3-PC	<0.2
1-Hexadecyl-1,3-propanediol-3-PE	7.8
1-Hexadecyl-1,3-propanediol-3-phosphoglycol	3.2
2-Tetradecyl-*rac*-G-3-PE	7.4
1-Octadecyl-1,3-propanediol-3-phosphate	<0.2

[a] G-3-PC and G-3-PE denote glycero-3-phosphocholine and glycero-3-phosphoethanolamine, respectively.

strate for the enzyme, which may explain its high toxicity for normal cells. Analogues with a free hydroxyl group in the *sn*-2 position, like 1-hexadecyl-*sn*-glycero-3-phosphocholine **54**, are better substrates. The enzyme does not exhibit any pronounced stereoselectivity, because the stereoisomer 3-hexadecyl-*sn*-glycero-1-phosphocholine **55** is cleaved approximately at the same rate as the substrate **54** with natural configuration. Neither of the two compounds are useful as antitumor drugs because they are detoxified not only by the 1-*O*-alkyl cleavage enzyme that is only found in normal cells, but also by acyl transferases[106] (for the compound **54** in natural configuration) as well as phospholipases C and D.

By careful study of the phospholipid-metabolizing enzymes of rat liver we were able to construct a cytotoxic lysophospholipid structure that cannot be modified or detoxified by acyl transferases, nor by the phospholipases C and D. This phospholipid, 1-hexadecyl-*sn*-glycero-3-phosphotrimethylammoniohexanol **56**, can only be degraded by the 1-*O*-alkyl cleavage enzyme[36].

At present, this cytotoxic phospholipid with an increased nitrogen-phosphorus separation is undergoing evaluation in animal tests. It is to be expected that the compound will be markedly less toxic for normal cells, which can degrade it biologically, than for tumor cells, which cannot. These examples illustrate how knowledge about the physical and biochemical properties of phospholipids can be used to synthesize tailor-made structures that are optimally designed for highly specific effects.

6. Concluding Remarks

From recent model studies using defined phospholipids, a new understanding of the role of phospholipids in biological membranes has evolved. In contrast with classical views, phospholipids are not merely a matrix that supplies the two-dimensional bilayer required by active membrane processes. They are functional building blocks that interact with other membrane components to induce biological activity. We know that their chemical structure can influence or even control membrane processes, such as ion transport or the activity of phospholipid-dependent enzyme systems. Thus, the physical properties of phospholipids, their phase transitions, and phase separations, become important elements of cellular function and regulation.

The cancer problem is one of the urgent challenges of our time. New therapeutic approaches are opened by simple modifications of phospholipid structures, which are sensitively detected by phospholipid-metabolizing enzymes. This is particularly promising where healthy and malignant tissues differ in their enzymatic equipment.

The therapy of brain tumors may profit from the observation that non-toxic alkyl glycerides can gently increase permeation of active substances across the blood-brain barrier. The range of molecular weights for which transport across the barrier membranes can occur is increased from 500 to 1500. This opens a vast horizon of possibilities for improving the lipophilic and membrane associating properties of drugs by chemical modification.

In closing, I would like to quote from a work written in 1796 and entitled "Die Kunst, das menschliche Leben zu verlängern" (The art of prolonging human life), written by *Christoph Wilhelm Hufeland*, who was the medical adviser to personalities such as *Goethe, Herder, Wieland,* and *Schiller*. In his words, a medicine may be called 'natural' if 'without tangible properties or detectable change of the organism, it quietly and gently, like nature herself, still brings forth the most desirable effects in the organism'. In this sense, *Kunze* et al.[110] have termed lecithin a true natural physic, that 'like sun, light, air, water or earth always acts beneficially, and in very many acute afflictions is indicated as an aid to the physician's treatment'.

Today, we have a more realistic view of the properties of phospholipids. Nevertheless, we are convinced that chemically defined phospholipids are useful model systems for the study of the properties of biological membranes. They help us to recognize transport mechanisms that can improve permeation across the lipid bilayer. Certainly, simple modifications of phospholipids, and the frequently surprising new properties that they bring about, will become important tools in developing new medications.

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Chemical Bonding in Higher Main Group Elements

By Werner Kutzelnigg*

Many concepts used for a qualitative description of chemical bonding that originated in the early days of theoretical chemistry have been vindicated recently by quantum chemical calculations, at least as far as first row elements are concerned. However, many concepts that have been justified for first row elements (Li to Ne) cannot—contrary to widespread belief—be generalized to the higher main group elements. This applies particularly to the concept of hybridization, which should be viewed with considerable caution. The essential difference between the atoms of the first and higher rows is that the cores of the former contain only s-AOs, whereas the cores of the latter include at least s- and p-AOs. As a consequence, the s and p valence AOs of first row atoms are localized in roughly the same region of space, while the p valence AOs of higher row atoms are much more extended in space. This has the consequence that for the light main group elements both lone-pair repulsion and isovalent hybridization play a greater role than for the heavy main group elements. Furthermore, this implies that single bonds between first row elements are weak and multiple bonds are strong, whereas for the second or higher row elements single bonds are strong and multiple bonds weak. The "extended valence" (violation of the octet rule) observed in compounds of higher main group elements has very little to do with the availability of d-AOs but is due rather to the size of these atoms and thus to the reduced steric hindrance between ligands and, to a lesser extent, also to the lower electronegativity of the heavy atoms. A model based on the concept of electron-rich multicenter bonds is certainly closer to reality than one involving hybrids with the participation of d-AOs. The XO bonds in phosphane oxides, sulfoxides, oxo acids and related compounds are better formulated as semipolar rather than as true double bonds, even if they behave in some respects like double bonds.—The growing interest of theorists in compounds of higher main group elements parallels new and, in some instances, spectacular results of experimental research on the chemistry of these elements.

1. Introduction

The molecular chemistry[1] of higher main group elements has advanced in an unexpected and fascinating way in recent years. We point out here the synthesis and characterization of compounds with "genuine"[2] double bonds involving elements such as Si or P[4–16] and which were long thought not to exist, e.g. SiC[7–9], SiSi[10,11], or PP double bonds[12–16]. Furthermore, we mention the relatively young chemistry of phosphorus chains, rings, and polycyclenes[17], e.g. the synthesis of a substituted tetraphosphabicyclobutane[18] and progress in the chemistry of hypervalent compounds with "non-genuine"[2] double bonds, such as OSF_2[19], $RNSF_4$[20–22], H_2CSF_4[23], and even triple bonds as in NSF_3[24].

Parallel to this progress in experimental research, quantum chemistry has also directed its interest to the higher main group elements. This has been possible, on the one hand, due to ab initio programs which are capable of dealing with the large number of electrons in heavy atoms and, on the other, because of the improvement of "pseudopotential methods". In applying the latter methods, the atomic cores are not explicitly considered, and it suffices to study the valence electrons moving in an "effective field"; consequently, a calculation on SnH_2 requires no more computer time than that for CH_2 (cf. also Section 2.4).

Semiempirical procedures (e.g. of the CNDO type), which have proved highly successful for first row atoms, have not performed so well for higher row atoms, mainly because it is highly problematic to fix the parameters for d-AOs. Therefore, reliable information on d-AO participation in the bonding can only be obtained from ab initio calculations.

In the meantime, relativistic calculations have also become feasible and for very heavy atoms, e.g. Pb, these are indispensable. Broadly speaking, relativistic quantum mechanics is a combination of ordinary quantum mechanics and the theory of special relativity. It is well-known that classical mechanics provides only an approximate description of the motion of particles and that the approximation becomes increasingly good the lower the velocity (relative to the velocity of light) and the larger the dimension of the motion (relative to atomic dimensions, e.g. bond lengths). For motions in atomic dimensions (but at low velocities) quantum mechanics rather than classical mechanics must be used, whereas for motions at high velocities (but in macroscopic dimensions) classical mechanics must be replaced by the theory of special relativity. For motions in atomic dimensions with velocities approaching the velocity of light, relativistic quantum mechanics must be used; this

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includes both ordinary quantum mechanics and the theory of special relativity as special cases.

The 1s electrons in the atoms of elements of the highest rows attain velocities quite comparable to the velocity of light, and hence only relativistic quantum mechanics is appropriate. Its formulation for many-electron systems is still not finally settled[25], although relativistic Hartree-Fock calculations are certainly possible; these clearly indicate that the differences in the chemical behavior of the fourth and fifth row elements (Rb to Xe and Cs to Rn) is determined decisively by relativistic effects. For lighter atoms, however, relativistic effects (of which spin-orbit coupling and the "velocity-mass correction" are most important) play only a minor role. The significance of relativistic effects in chemistry—especially for atoms of the fifth row—has been discussed in several recent articles[26–28].

The exceptional behavior of first row elements, which is of particular concern to us in this review, has nothing to do with relativistic effects.

In view of the renewed interest in molecules of main group elements of the second and higher rows, the question of the bonding in these molecules has again become a topical issue. Long ago, *Pauling*[29] clearly recognized the differences in chemical behavior between first (Li to Ne) and higher row elements and offered a plausible explanation. Yet the theory of chemical bonding, as presented in modern textbooks, still concentrates mainly on the main group elements of the first row (and on the transition elements of the third row). It is customary to regard the bonding of the atoms from Li to Ne as normal and thus to consider the behavior of the heavy elements as "abnormal". Later on in this article we shall reach the conclusion—which we anticipate here—that it is rather the heavy elements which behave normally and not the more familiar elements of the first row.

In this progress report we seek to answer why differences exist in the chemical bonding of main group elements of the first and higher rows in the light of recent data and quantum-chemical calculations. From the wealth of interesting findings and their interpretation, we select a few which appear to be of fundamental importance:

1. For any series of compounds of first row elements, the analogous compounds of higher row elements have different geometries and other physical properties. Examples are provided by the pairs H_2O/H_2S or NH_3/PH_3 and also CH_2/SiH_2.
2. Certain types of bonding commonly found between light atoms occur only rarely in elements of the higher rows, e.g. multiple bonds. The different capabilities of C and Si to form double bonds, which makes the chemistry of carbon and of silicon fundamentally different, is most striking.
3. Certain other types of bonding are found only in heavy atoms, especially in hypervalent compounds such as PF_5 or SF_6.
4. Finally, there are bonds which although formally the same in elements of the first and higher rows are, nevertheless, very different, e.g. the semipolar bonds in R_3NO and R_3PO.

Furthermore, it is worthwhile to study the difference between "genuine" and "non-genuine" multiple bonds[2]. This will be discussed within the context of points 2 and 4.

2. Differences in the Isolated Atoms of Homologous Main Group Elements

2.1. Orbital Energies

The energy levels of s, p, and d atomic orbitals (AOs) for elements of the first, second, and third rows are depicted schematically in Figure 1. In each group a marked jump is apparent in proceeding from the first to the second row, whereas there is little change between the second and higher rows (apart from a larger spin-orbit splitting between the $p_{1/2}$ and $p_{3/2}$ levels for the very highest rows, which we have not documented here).

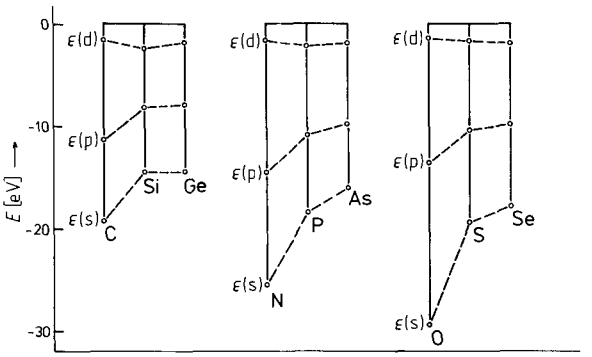

Fig. 1. Energies of s, p and d valence AOs for some main group elements. The ε(p) values given are equal (except for the sign) to the experimental ionization potentials for ionization from a p-AO. ε(s) is equal to ε(p) minus the lowest s→p excitation energy (with conservation of spin multiplicity). Correspondingly, ε(d) is equal to ε(p) plus the lowest p→d excitation energy (with conservation of spin multiplicity). The Hartree-Fock orbital energies differ by only a few eV from the ε(s) and ε(p) used here. All of the data have been taken from *Moore*'s tables [31]. According to *Mulliken* [32], there is a relationship between ionization potentials and electronegativities.

If one assumes that the lower the promotional energy the more readily hybridization occurs, one would expect more hybridization in heavy atoms—contrary to what is observed.

2.2. Size of Atoms

The "size" of an atom is very important for its chemical behavior. A possible measure of this is the expectation value (mean value) $\langle r \rangle$ of the distance of the valence electrons from the nucleus. Quantum-chemically calculated[30] values of $\langle r \rangle$ for s and p valence AOs are depicted in Figure 2.

For elements of the fourth and fifth main groups, the calculated $\langle r \rangle_s$ values agree well with *Pauling*'s[29] covalent radii; however, they vary strongly as a function of the group and are larger in the third and smaller in the seventh group than *Pauling*'s empirically determined radii.

First, it should be noted that $\langle r \rangle_s$ and $\langle r \rangle_p$ for the first row differ little from one another (by ca. 10%), whereas for

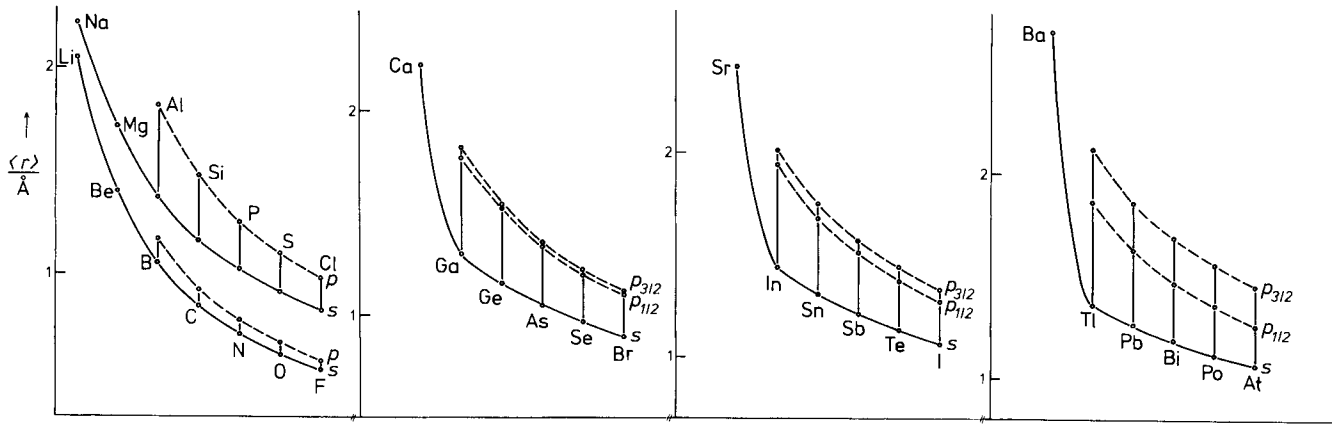

Fig. 2. Expectation values $\langle r\rangle_s$ and $\langle r\rangle_p$ for s and p valence AOs. The indices 1/2 and 3/2 associated with the p-AOs characterize the two components arising from spin-orbit coupling (cf. text). The values given are obtained from relativistic Hartree-Fock calculations by *Desclaux* [30].

higher rows the differences are more pronounced (20—33% for the second row; 24—40% for the third and fourth rows; and 36—55% for the fifth row).

Furthermore, we observe that $\langle r\rangle_{p3/2}$ and $\langle r\rangle_{p1/2}$ differ from each other by less than 2% for the first three rows, by ca. 5% in the fourth row, and by as much as ca. 15% in the fifth row. Within the framework of "ordinary" nonrelativistic quantum mechanics, such as in conventional Hartree-Fock calculations, there is no difference between $p_{1/2}$ and $p_{3/2}$, and the p level is sixfold degenerate (threefold orbital degeneracy and a twofold spin degeneracy). The splitting into a twofold degenerate $p_{1/2}$ and a fourfold degenerate $p_{3/2}$ level is a relativistic effect which depends on so-called spin-orbit coupling. In the fifth row, the two possible p states differ from each other almost as much as the s and p (the effect is even more marked in the orbital energies than in the radii). This relativistic effect has major consequences for the chemical behavior of the very heavy elements[26–28].

In simple terms, it may be said that the s and p valence electrons in first row atoms occupy roughly the same region of space, whereas p-type valence electrons in higher row atoms are considerably more diffuse than the corresponding s-type AOs.

The reason for the different "size" of s and p valence orbitals is not readily understandable[33]. In Section 2.4 we offer a simple explanation in terms of the pseudopotential model.

One should not take the $\langle r\rangle$ values in Figure 2 too literally. These are based on relativistic SCF calculations[30], i.e. although relativistic effects are taken into account, the SCF approximation has been made. Thus, each electron has been assigned a one-electron function (an orbital), and the repulsion between the electrons has only been treated on the average. A precise determination of the electronic interactions is very cumbersome and only tractable within the framework of the configuration interaction (CI) method or the coupled electron pair approximation (CEPA)[34]. The effects neglected in the SCF approximation are designated "electron correlation"[34]. Electron correlation actually has a noticeable influence on the "size" of the atom (i.e. on the mean radii $\langle r\rangle_s$ and $\langle r\rangle_p$), especially for alkali metal and alkaline earth atoms (where the electron correlation reduces $\langle r\rangle$ by 10%[37]), but to a lesser extent for atoms of the fourth to the sixth main groups. At any event, $\langle r\rangle_s$ and $\langle r\rangle_p$ are computed parameters that cannot be directly compared with measured physical quantities.

2.3. Polarizabilities

Another relevant property of an atom is its polarizability (Table 1). Correlation effects have been taken into consideration. Polarizabilities change substantially on proceeding from the first to the higher rows. Even more pronounced is the dependence on the group in the periodic system. If we confine ourselves to groups 3b to 5b, a significant jump in going from the first to the second row is evident.

Table 1. Dipole polarizabilities in atomic units (1 a.u. = 0.1482 Å^3) [a].

Li	Be	B	C	N	O	F	Ne
164.5	37.8	20.5	11.8	7.4	5.4	3.8	2.7
Na	Mg	Al	Si	P	S	Cl	Ar
165.0	71.3	56.3	36.3	24.5	19.6	14.7	11.1
K	Ca	Ga	Ge	As	Se	Br	Kr
287.6	153.9	54.8	41.0	29.1	25.4	20.1	16.7
Rb	Sr					I	Xe
333.0	169					(34)	27.3
Cs	Ba						
416.5	209						

[a] For the atoms from Li to Ca the values are taken from accurate quantum-chemical calculations by *Werner* and *Meyer* [136] or *Reinsch* and *Meyer* [137] (CEPA-calculations, considerating intershell correlation effects); for Rb and Cs they are taken from *Maeder* and *Kutzelnigg* [37] (pseudopotential calculations); for Ge to Br they are from *Miller* and *Bederson* [138]; and for the remaining atoms they are taken from *Teachout* and *Pack* [139]. The experimentally determined values of *Molof* et al. [140] are very similar for the alkali metal atoms.

2.4. Pseudopotentials

The mere existence of a periodic system of the elements suggests that only the valence electrons are directly responsible for the chemical behavior of atoms, whereas the core electrons merely provide a sort of effective potential in which the valence electrons move. *Hellmann*[38] and, independently, *Gombas*[39] were the first to formulate this

quantitatively and to develop simple expressions for the "effective potential". This potential must also account for the Pauli exclusion principle in the sense that the valence AOs must be orthogonal to the core AOs; this can be represented by a repulsion which prevents the valence electrons from "penetrating" into the core and which counterbalances the increased (less shielded) attraction by the nucleus in the neighborhood of the core.

The effective potential "felt" by the valence electrons is usually designated a "pseudopotential" or "model potential"[40].

Although the pseudopotential approximation is not exact—in particular, as far as transferability of atomic pseudopotentials to molecular problems is concerned—it is in most instances an astonishingly good approximation.

According to their analytical form, one can distinguish between three types of pseudopotentials; "local", "semilocal", and "nonlocal". A local pseudopotential is—like a genuine potential—simply a function $V(r)$ of the distance r of the electron from the nucleus (for large r this function behaves like the Coulomb potential for the nuclear charge shielded by the core electrons and for small r allows for "penetration" and "Pauli repulsion"). A nonlocal pseudopotential can be defined only as an integral operator (similar, for example, to the exchange operator in Hartree-Fock theory). Most pseudopotentials used today are of the "semilocal" type

$$V = \sum_l V_l(r) P_l \tag{1}$$

where l counts the angular quantum number ($l=0$ corresponds to s-AOs, $l=1$ to p-AOs, etc.) and P_l is a so-called projection operator on the AOs for that l. For each fixed value of l, the pseudopotential is so-to-speak "local". If $l>2$ (or $l>1$) and $V_l(r)$ is chosen as a simple Coulomb potential independent of l, only $V_0(r)$ (for s-AOs), $V_1(r)$ (for p-AOs) and, if necessary, $V_2(r)$ remain to be determined. In principle, there are two possibilities for determining pseudopotentials (or the parameters which characterize them); namely, either from ab initio calculations which include all electrons or by semiempirical fitting to experimental data.

For example, one can choose a form for V_0 and V_1 containing in each case only one free parameter which can then be determined[37] such that the lowest experimental ionization potentials for s- and p-AOs are correctly reproduced. Using such a semiempirical 2-parameter potential, one can for alkali metal and alkaline earth atoms not only accurately describe the "size", polarizability, frequencies, and oscillator strengths characterizing the electronic spectrum[37] but also use this pseudopotential for calculations on molecules[51].

This indicates that it is quite reasonable to approximately describe the difference in the chemical behavior of homologous atoms in terms of two parameters only. These could, for example, be the different ionization potentials for the s and p valence electrons or the different spatial extension of the s and p orbitals.

From a purely theoretical standpoint, ab initio pseudopotentials are more satisfying than semiempirical model potentials. The first ab initio pseudopotentials have been fitted to all-electron SCF calculations. SCF calculations based on these pseudopotentials and limited to valence electrons reproduced many results obtained using all-electron SCF calculations, resulting in considerably less computational effort[43-46]. However, agreement with experiment was usually less satisfactory than that for semiempirically adjusted pseudopotentials since the latter implicitly include relativistic effects as well as so-called core polarization. Because it is also now possible to obtain relativistic ab initio pseudopotentials[47,48], and ab initio procedures to calculate the core polarization are available[49], we expect that ab initio pseudopotentials will dominate in the future.

All-electron ab initio calculations are still out of the question for higher row elements because of the vast number of electrons involved. Pseudopotentials, however, can be very valuable here. The increasing interest in compounds of the heavy elements and the gain in theoretical insight in the past decade have been accompanied by progress in pseudopotential theory.

Within the framework of the pseudopotential model it is possible, as already mentioned, to rationalize the different, relative spatial distributions for the s and p valence electrons of the first and higher rows. To avoid any discussion of the interactions between valence electrons, we shall consider systems having only a single valence electron, i.e. alkali metal atoms. The wave function $\psi_{nlm}(r)$ is a product of two factors: a radial function $f(r)$ and an angular function $Y_l^m(\theta,\phi)$, a so-called spherical harmonic[52]. The radial function $f(r)$ is the solution of the "radial Schrödinger equation" (in atomic units[52])

$$-\frac{1}{2r^2}\frac{\mathrm{d}}{\mathrm{d}r}r^2\frac{\mathrm{d}f(r)}{\mathrm{d}r} + U_l(r)f(r) = \varepsilon f(r) \tag{2}$$

where the effective radial potential $U_l(r)$ consists of the pseudopotential $V_l(r)$ and a so-called centrifugal potential $Z_l(r)$:

$$U_l(r) = V_l(r) + Z_l(r)\,; \quad Z_l = \frac{l(l+1)}{2r^2} \tag{3}$$

The pseudopotential $V_l(r)$, in turn, can be resolved into a Coulomb potential $-1/r$ (in the field of the nucleus shielded by the core) and an additional potential $W_l(r)$ which takes into account both the partial penetration of the valence electron into the core and the "Pauli repulsion" (or "Fermi repulsion"), i.e. the required orthogonality to the core states.

$$V_l(r) = -\frac{1}{r} + W_l(r)\,; \quad U_l(r) = -\frac{1}{r} + W_l(r) + Z_l(r) \tag{4}$$

Whenever the additional potential $W_l(r)$ is approximately the same for $l=0$ (s-AOs) and $l=1$ (p-AOs), the centrifugal potential $Z_l(r)$ (which vanishes for $l=0$ and is strongly repulsive for $l=1$) ensures that the lowest p valence AO has a significantly higher energy, and is on average markedly further from the nucleus than the lowest s valence AO.

To a very good approximation this holds for Na, K, Rb, and Cs, since here both $W_0(r)$ and $W_l(r)$ are strongly repulsive in the core region because of the orthogonality requirement to the occupied core states with $l=0$ or $l=1$.

This does not apply to Li, where only one s-AO but no p-AO is occupied in the core. As a consequence, $W_0(r)$ is strongly repulsive in the core region, whereas $W_l(r)$ is even weakly attractive owing to the reduced shielding of the nuclear charge in the core region (which is also present in other cases, but is more than compensated for by the Pauli repulsion). The effective radial potentials $U_l(r)$ are now comparably repulsive for s and p, and thus the radial functions are located in roughly the same region of space. Since $W_0(r)$ is of shorter range than $Z_l(r)$, $\varepsilon(2s)$ is distinctly lower than $\varepsilon(2p)$, although in relative terms not as low as in the other alkali metal atoms.

Put simply, atoms of the first row are special because only s-AOs are occupied in their cores and consequently the p-AOs experience no Pauli repulsion from the core. This is not the case for heavy atoms whose cores contain occupied s- and p-AOs.

This difference is fully taken care of within the framework of nonrelativistic quantum mechanics; the pronounced contraction of the 6s orbitals, which is principally responsible for the differences between atoms of the fourth and firth rows, is, however, a relativistic effect[26-28].

3. Electronic Structure and Equilibrium Geometry of Molecules with Normal Valencies

3.1. Hybridization and Valence Configurations

In the following discussion, frequent use will be made of the concept of "hybridization". This was developed during the early days of theoretical chemistry and is still very popular among experimental chemists. Modern quantum chemistry, however, has no real place for it, and many theoretical chemists regard it as problematic or as outdated. Nevertheless, several recent studies indicate a renewed interest in a formal discussion of hybridization[53,54]. The concepts of valence state and of hybridization—which are closely related—arose originally within the context of the valence bond (VB) approximation[55]. In terms of these concepts, it was possible to explain, e. g., the tetravalence of carbon by assuming that the C atom is first "excited" from the ground state (^3P_g) configuration $1s^2 2s^2 2p^2$ into the valence state configuration $1s^2 2s^1 2p^3$ (with all the spins of the valence electrons uncoupled) and then hybridization from sp^3 to te[4] takes place.

In the molecular orbital (MO) approximation, there is no need for ad hoc assumptions about hybridization. In fact, it is possible to manage without this concept at all. For CH_4, for example, if one starts from a so-called minimal AO basis set consisting of one 1s AO per H atom and a $1s,2s,2p_x,2p_y,2p_z$ set for the C atom, the tetravalence of carbon arises automatically.

If desired, the concepts of "valence configuration" (this is preferable to that of the "valence state"[56]) and hybridization may be used in conjunction with MO calculations for an a posteriori interpretation of the results. This is done via a so-called population analysis as described by *Mulliken*[58], although it must not be forgotten that the results of such an analysis are somewhat dependent on the chosen basis set[59]. *Mulliken*'s gross atomic populations (occupancy numbers), $q_s(X)$ or $q_p(X)$, are a measure of the probability of finding an s or p-AO on atom X.

If the occupancy number (gross population) of, for example, the 2s-AO on the C atom in CH_4 has the value $q_s=1.12$ and for all the 2p-AOs together $q_p=3.09$, we can then state that the valence configuration is $2s^{1.12}2p^{3.09}$. It is evident that this configuration deviates substantially from the $2s^2 2p^2$ ground configuration but that it lies close to the "ideal" valence configuration $2s2p^3$[56].

At first sight, this definition may appear to be meaningful only if a "minimal" AO-basis set has been employed. In general, such minimal basis sets yield very poor results. When use is made of larger basis sets, however, it is possible to sum up both s- and p-type populations and thereby express the valence configuration in terms of these total s- and p-AO populations, bearing in mind that two s-AOs or four s-AOs and six p-AOs, etc. must be deducted for the cores. All the valence configurations discussed in this article were determined in this way based on SCF calculations with sufficiently large basis sets[61].

The concept of hybridization is then meaningful in the analysis of the results of MO calculations whenever a description of the molecule in terms of two-center MOs is possible. In fact, it has been found for most "normal" molecules (for limitations see [62]) that the delocalized, so-called canonical MOs can be transformed by means of a unitary transformation[63] (for example, as proposed by *Boys*[65]) to yield localized molecular orbitals (LMOs) which are localized mainly in a bond. The overall wave function is not changed in the procedure[63].

If separate population analyses are carried out for each LMO, statements on the nature of the mixture of s, p, and d valence AOs can be made, i.e. which hybrid AO is involved in a given bond. According to our calculations, the s : p ratio for methane is 1 : 2.76, which is very close to the ratio for a tetrahedral sp^3 hybrid.

Let us suppose that the LMOs for two equivalent XH bonds in an XH_n molecule are as follows

$$\varphi_1=\alpha\,hy_1+\beta\,h_1 \tag{5a}$$

$$\varphi_2=\alpha\,hy_2+\beta\,h_2 \tag{5b}$$

where hy_1 and hy_2 signify two hybrid AOs of the X atom and h_1 and h_2 are two 1s-AOs of H atoms. The LMOs are assumed to be "well localized", i.e. the contributions of the "other" h_k to the φ_l ($k\neq l$) are regarded as negligibly small. Since MOs must be orthogonal, i.e. their overlap integral $\langle\varphi_1|\varphi_2\rangle$ must vanish, it follows that

$$\langle\varphi_1|\varphi_2\rangle=\alpha^2\langle hy_1|hy_2\rangle+\alpha\beta\{\langle hy_1|h_2\rangle+\langle hy_2|h_1\rangle\}+\beta^2\langle h_1|h_2\rangle=0 \tag{6}$$

As a rule, the overlap integrals $\langle h_1|h_2\rangle$ between different H atoms are very small. We regard hybrids as "good" or as "ideally directed" if they bond in only one direction, i.e. if

$$|\langle hy_1|h_1\rangle| \gg |\langle hy_1|h_2\rangle| = \langle hy_2|h_1\rangle. \tag{7}$$

If the overlap integrals $\langle hy_1|h_2\rangle$ for a hybrid AO with the "wrong" H atoms vanish (and if also $\langle h_1|h_2\rangle \approx 0$), it follows from equation (6) that

$$\langle hy_1|hy_2\rangle \approx 0 \tag{8}$$

which implies that the various hybrids on an atom are mutually orthogonal. The orthogonality of the hybrids can be regarded almost as a criterion for "good hybrids". Since the initial AOs on the atom, e.g. the 2s and 2p, are mutually orthogonal, orthogonal hybrids are obtained from these by an orthogonal transformation[63]. This is normally tacitly implied whenever one speaks of hybrids. With the prerequisite that hybrids are mutually orthogonal, it is possible to formulate a relationship between the degree of hybridization and the valence angle[67]. The following relationship holds for an angle θ between equivalent hybrids (i.e. hybrids with the same s contribution)

$$\cos\theta = -a^2/(1-a^2) \tag{9}$$

where a^2 is the s contribution to the hybrid and $1-a^2$ is thus the p contribution.

In the context of this relationship, it is nowadays almost taken for granted that, for example, a bonding angle of 120° implies an s contribution of $a^2 = 1/3$ and accordingly sp^2 hybridization.

As shown in Section 3.3, such conclusions based on the assumption of orthogonal hybrids are fairly reliable for compounds of first row elements only, but are dubious for higher row main group elements. Therefore, equation (9) is a good approximation only for molecules consisting of atoms Li to F.

From the population analyses, information is also obtained about the charges associated with the atoms in molecules and thus about the polarity of bonds. For the previously mentioned calculations on CH_4, one obtains $q_s + q_p = 4.21$ compared to 4 in the ground configuration; accordingly, the C atom bears a formal charge of -0.21[68].

3.2. Bonding Energies of Monohydrides XH and "Saturated" Hydrides XH_n

The bonding energies of a series of monohydrides, XH, together with the energy contributions per XH bond in the "saturated" hydrides, XH_n are shown in Figure 3. It is immediately apparent that the values of the bonding energies per XH bond in XH_n for X = C, N, and O are larger than those in the respective monohydrides by 18, 15, and 10 kcal/mol, respectively. The corresponding "bond strengthenings" for X = Si, P, and S amount to roughly 6 kcal/mol. For BeH_2 compared to BeH and MgH_2 compared to MgH, the bond strengthenings are even higher, but again the effect for Be is substantially larger than that for Mg. It is worth commenting that for the fluorides (cf. Fig. 9) the relationships are quite different, a point which we shall return to in Section 3.9. The bond strengthenings for BeH_2 and MgH_2 are explained in Section 3.4 and those for other compounds in Section 3.6.

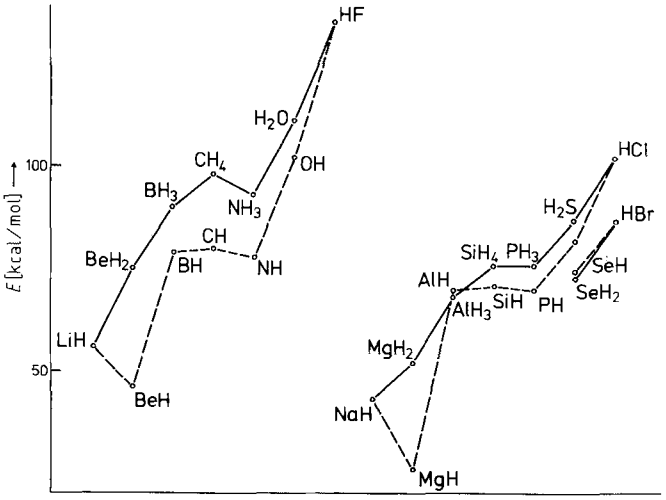

Fig. 3. XH bond energies for monohydrides and saturated polyhydrides of main group elements (for the sources of the values cf. Appendix 1).

Similar trends are found in the bond lengths[69]. Thus, in proceeding from the monohydrides XH to the polyhydrides XH_n the XH bond lengths are reduced by a few percent, both for X from the first and second rows. The effect, however, now varies strongly with the group in the periodic table (5% for BH and CH but only 1% for OH).

3.3. Hybridization and Polarity in the Hydrides BeH_2, BH_3, and CH_4 Compared to MgH_2, AlH_3, and SiH_4

The populations of the s, p, and d valence AOs on the central atom are depicted for the molecules BeH_2, MgH_2, BH_3, AlH_3, CH_4, and SiH_4 in Figure 4. In these XH_n molecules the ratios of the s and p populations lie between the values for the ground configurations (GC) of X without promotion and those for "ideal" sp^{n-1} hybridization. The values for molecules of elements from the first row (Be, B, C) lie much closer to those for ideal hybridization than the values for molecules of elements from the second row (Mg, Al, Si).

If one is accustomed to believe that in a planar XH_3 molecule such as BH_3 or AlH_3 sp^2 hybridization of the central atom is inevitable, one is surprised that in AlH_3 the s : p ratio is only 1 : 1.15, whereas in BH_3 it is at least 1 : 1.64 and not so far removed from the expected 1 : 2.

To analyze the problem more closely, we investigated the molecules BeH_2 and MgH_2. Although these are of less interest to chemists, they can be treated in a formally more straightforward way than XH_3 or XH_4 molecules[72].

MO calculations on BeH_2 or MgH_2 yield, in addition to MOs characterizing the cores of Be ($1s^2$) or Mg ($1s^2 2s^2 2p^6$), canonical valence MOs having the form:

$$\psi_1 = c_1 s + c_2 h_1 + c_2 h_2 \tag{10a}$$

$$\psi_2 = c_3 p + c_4 h_1 - c_4 h_2 \tag{10b}$$

where the s and p valence AOs of the Be or Mg are, respectively, of s or p_z type (z = molecular axis), and h_1 and h_2 represent s-AOs for the two H atoms. Normally, AO basis

sets with more than four functions are employed, though the result can still be presented in the form (10a, b), where s, p, h_1 and h_2 are no longer identical to the corresponding functions in the isolated atoms. Strictly speaking, even h_1 and h_2 in (10a) and (10b) are not identical, but their difference is not of importance here.

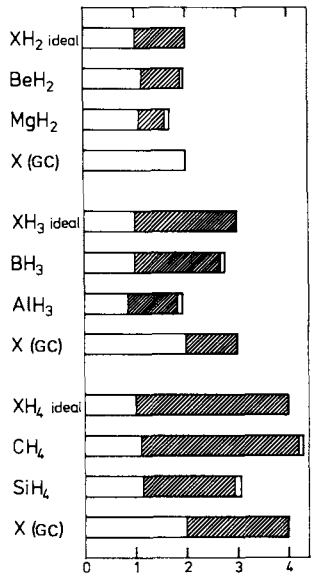

Fig. 4. Mulliken gross populations for the valence AOs of X in XH_n molecules without lone pairs of electrons. From left to right: s, p (hatched), d. The populations given as "XH_n ideal" obtained formally from the valence angles, assuming orthogonal hybrids. X(GC) indicate the ground configuration of the isolated atom. The populations are based on SCF calculations with a 9/5/1 Gauss basis for Be, B, C; an 11/7/1 basis for Mg, Al, Si; and a 5/1 basis for H in triple zeta contraction in each case. The exponents are taken from *Huzinaga* [147]; and for d and p_H from *Ahlrchs* et al. [78, 143].

The total wave function remains invariant[63] if the doubly occupied canonical MOs ψ_1 and ψ_2 are replaced by the so-called equivalent MOs φ_1 and φ_2 which are related to ψ_1 and ψ_2 as

$$\varphi_1 = \frac{1}{\sqrt{2}}(\psi_1+\psi_2) = \frac{c_1}{\sqrt{2}}s + \frac{c_3}{\sqrt{2}}p + \frac{(c_2+c_4)}{\sqrt{2}}h_1 + \frac{(c_2-c_4)}{\sqrt{2}}h_2 \quad (11a)$$

$$\varphi_2 = \frac{1}{\sqrt{2}}(\psi_1-\psi_2) = \frac{c_1}{\sqrt{2}}s - \frac{c_3}{\sqrt{2}}p + \frac{(c_2-c_4)}{\sqrt{2}}h_1 + \frac{(c_2+c_4)}{\sqrt{2}}h_2 \quad (11b)$$

The ideal case where s and p bond "equally" with h_1 and h_2 is characterized by:

$$c_1 = c_3\,; \quad c_2 = c_4 \quad (12)$$

and the equivalent MOs are then

$$\varphi_1 = \frac{c_1}{\sqrt{2}}(s+p) + c_2\sqrt{2}\,h_1 \quad (13a)$$

$$\varphi_2 = \frac{c_1}{\sqrt{2}}(s-p) + c_2\sqrt{2}\,h_2 \quad (13b)$$

i.e. they are genuine two-center MOs formed from one sp hybrid AO and the s-AO of one of the H atoms in each case.

In practice, the relationship (12) is never strictly fulfilled. When the absolute value of the "localization defect"

$$d_l = \frac{c_2-c_4}{c_2+c_4} \quad (14)$$

is small, the description of the molecule in terms of localized two-center bonds is a good approximation, irrespective of whether the "hybridization defect"

$$d_{hy} = \frac{c_1-c_3}{c_1+c_3} \quad (15)$$

is also small. If $|d_{hy}|$ is small, the formulation of (13) with two mutually orthogonal hybrids proves to be a good approximation. However, if $|d_{hy}|$ is not small, the hybrid AOs involved in each XH bond as defined in (11) are not mutually orthogonal, i.e. their overlap integral $\langle hy_1|hy_2\rangle = (c_1^2-c_3^2)/(c_1^2+c_3^2)$ can become quite large.

For BeH_2 and MgH_2 we obtained the following values

BeH_2: $d_l = -0.065$; $d_{hy} = 0.055$; $\langle hy_1|hy_2\rangle = 0.109$; $\langle h_1|h_2\rangle = 0.084$
MgH_2: $d_l = -0.092$; $d_{hy} = 0.183$; $\langle hy_1|hy_2\rangle = 0.354$; $\langle h_1|h_2\rangle = 0.042$

It is evident for all of the hydrides discussed in this section—and this is confirmed by comparisons of BH_3 with AlH_3, and CH_4 with SiH_4—that the magnitude of the localization defects is small. This means that a description in terms of localized XH bonds is justified, although the hybridization defect will be sufficiently small in absolute value only for BeH_2, BH_3, and CH_4 but not for MgH_2, AlH_3, and SiH_4. For the last three molecules, the hybrid AOs are far from orthogonal.

The s component in these hybrids (cf. Fig. 4) is much larger than that calculated from the valence angle given by equation (9). The hybridization defect is especially small in CH_4 ($d_{hy} = 0.08$; $\langle hy|hy'\rangle = 0.017$). Clearly, "good", i.e. optimally directed, hybrids are only possible if the s and p valence AOs are localized in roughly the same region of space. "Good" hybrids are those linear combinations of s- and p-AOs such that on one side of the nucleus the s and p components contribute additively while on the other side they almost cancel. This can only arise if the radial factors of s and p do not differ much.

It is somewhat surprising that the XH bonds in MgH_2, AlH_3, and SiH_4 are highly localized, despite "poor" hybridization.

One explanation for this is that there is a strong displacement of electronic charge from X to H in the XH bonds of MgH_2, AlH_3 and SiH_4. One realizes that for ideal ionic bonding—such as in $Mg^{2\oplus}(H^{\ominus})_2$—the MOs for the MgH bonds are in fact localized, namely on the H atoms, irrespective of the hybridization at the Mg atom (for an ideal ionic bond $q_s = 0$ and $q_p = 0$ and the hybridization ratio is undefined). The s-p ratio at the central atom has little influence on the localizability, as long as the bond is strongly polar (with H the more negative atom), even if it is not ideally ionic. Hybridization has an effect on localizability as well as on the bond strength only in mainly covalent bonds.

3.4. Comparison of BeH and MgH with BeH_2 and MgH_2

The differences in the XH bonding energies shown in Figure 3 are especially striking for BeH and MgH monohydrides, on the one hand, and BeH_2 and MgH_2, on the other. For the sake of simplicity, let us suppose that the valence configuration of the Be and Mg is sp in both molecules (this is not strictly correct according to Section 3.3, cf. also Figs. 5 and 6). We shall also further suppose that promotion to the sp state is necessary to form a BeH or MgH bond. We can then set

$$\Delta E(XH_n) = E_{prom} + n E_{bond};\ n = 1, 2$$
$$E_{bond} = \Delta E(XH_2) - \Delta E(XH)$$
$$E_{prom} = 2\Delta E(XH) - \Delta E(XH_2)$$

where E_{bond} is the energy of a bond and E_{prom} is the promotion energy, and obtain

BeH/BeH_2: $E_{bond} = -104$ kcal/mol, $E_{prom} = 58$ kcal/mol
MgH/MgH_2: $E_{bond} = -78$ kcal/mol, $E_{prom} = 52$ kcal/mol

The lowest s→p excitation energy in Be and Mg atoms is 2.73 eV = 63 kcal/mol and 2.71 eV = 62 kcal/mol, respectively[31], and is of the same order of magnitude as the promotion energy estimated here.

3.5. Isovalent Hybridization in the Monohydrides

In Figure 5 the results of detailed population analyses of the monohydrides LiH to HF and from NaH to HCl are presented. BeH and MgH, which we discussed in Section 3.4, do not fit into the general pattern and nor do LiH and NaH. For these last-mentioned compounds, the valence AOs are essentially of s type, whereas for all the other molecules they are mainly of p type. The relatively strong s→p promotion in LiH and NaH is well understood, although it will not interest us further here.

A comparison of the overall s : p ratios (which are not readily apparent from Fig. 5) for BH to HF and for AlH to HCl reveals that for BH to HF an s→p excitation of ca. 0.1 to 0.35 electrons from the ground configuration occurs, whereas the corresponding excitation for AlH to HCl is ca. 0.0 to 0.23 electrons. As expected, this promotion is small and significantly smaller for second row than for first row atoms. Nevertheless, the conclusion that the promotion, and thus the hybridization, is negligible would be premature. Separate analysis for bonding MOs, unpaired electrons, and lone pairs of electrons (Fig. 5) indicates significant mixing of s components from X into the MO of the XH bond, which is often viewed as a purely p bond and even more mixing of p components into the lone pairs of electrons, which are usually expected to be pure s-AOs.

Any hybridization which does not increase the valence is referred to as isovalent. Essentially, there are two reasons for isovalent hybridization, as schematically illustrated in Figure 7:

(a) Hybrid AOs overlap better and form stronger bonds;

(b) By mixing p components with the lone pairs, the latter are displaced in the opposite direction to the XH bond, thereby reducing the "Pauli repulsion" ("Fermi repulsion") with the XH bonds.

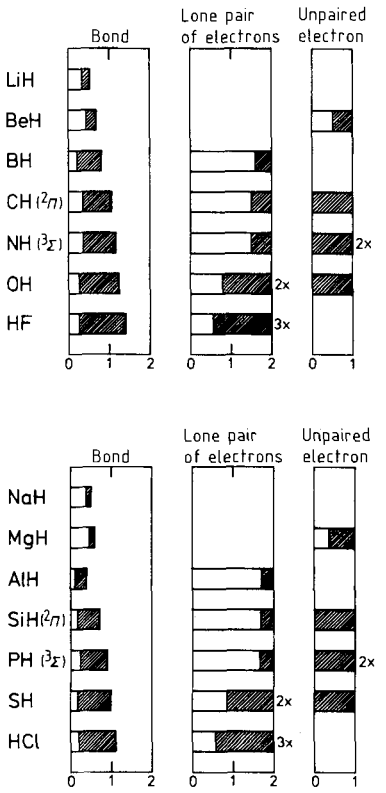

Fig. 5. Mulliken gross populations for the valence AOs of X in the localized MOs of monohydrides XH. Cf. legend to Figure 4. The populations of the d-AOs have not been sketched since they would not appear on the scale used here (they are smaller than 0.02).

The s→p promotion requires energy and there is competition between the gain in energy from hybridization and the loss in energy from promotion.

Of the two reasons given for isovalent hybridization, (a) is well-known[73a], whereas (b) requires some comment.

In the B atom, the (doubly occupied) 2s- and 2p-AOs are mutually orthogonal, i.e. their overlap integral is equal to zero. If an MO is now constructed for the BH molecule from the $2p_z$-AO of the B and an s-AO of the H, this MO is no longer orthogonal to the 2s-AO since the s-AO of H overlaps with the 2s-AO. Because the 2s-AO of B is doubly occupied (as is the MO we have constructed), the usual repulsion between doubly occupied orbitals occurs; this is often designated the Pauli force or exchange repulsion. This repulsion can be reduced by giving the lone pair an opportunity to move partially to the opposite side of the bond.

It is difficult to state whether effect (a) or (b) dominates. That both effects play a less significant role in, for example, AlH and thus contribute less than in BH may be readily seen from the different s : p ratios (cf. Fig. 5). Effect (a) is less important for higher row elements because the s valence AOs are less diffuse than the p valence AOs; mixing

of s components thus does not essentially improve the overlap capability. Moreover, because the s valence AO in AlH is less diffuse and the XH separation is greater than in BH, the Pauli force is also not so large; consequently, the lone pair of electrons is less likely to be displaced.

Since these two effects are less pronounced for the higher main group elements, less isovalent hybridization occurs in these elements. Here, differences in the bond polarities play only a minor role.

Mulliken overlap populations—which provide a measure of the strengths of covalent bonds—have not been documented here. The sh overlap populations are—apart from LiH, NaH, BeH, and MgH—negative and especially so in AlH, SiH, PH, and BH (values lie between -0.10 and -0.20). The interaction of the doubly occupied 2s- or 3s-AOs of the heavy atoms with the 1s-AO of the H atom is, as already explained, certainly repulsive or antibonding.

Since the ph overlap populations are positive and their magnitudes sufficiently large ($+0.30$ to $+0.40$), overall positive X–H overlap populations result with values lying between $+0.17$ (AlH) and $+0.33$ (HCl).

3.6. Pauli Repulsion and Isovalent Hybridization: The Valence Angles in NH_3 and H_2O Compared with Those in PH_3 and H_2S

Among the more spectacular differences between the compounds of elements of the first and higher rows are the geometries of, for example, H_2O and H_2S, H_2Se, etc. or of NH_3 and PH_3, AsH_3, etc. Whereas the valence angles in H_2O and NH_3 are ca. 104° and are thus almost tetrahedral, the valence angles in H_2S, H_2Se, PH_3, and AsH_3 are close to 90°. It is frequently assumed that the bonding in H_2S, PH_3, etc. involves almost pure p-AOs while in H_2O and NH_3 hybrid AOs are involved. This implies that extensive use of isovalent hybridization would be made for H_2O and NH_3 but not for H_2S and PH_3[73b].

Figure 7 demonstrates the reasons for isovalent hybridization. In Section 3.5 we have already mentioned that the effects (a) and (b) are important for diatomic molecules; to these we now add a third:

(c) Increase of the valence angle by hybridization and consequent reduction of the Pauli repulsion between the XH bonds.

That Pauli repulsion between the XH bonds occurs independently of any assumptions about hybridization can be demonstrated, for example, by artificially inhibiting hybridization in a calculation[74] in which the 2s-AO (or 3s-AO) is "frozen in"[75] so that its population remains at $q_s = 2$. Although the XH bonds will then be provided by pure p-AOs, the HOH angle in H_2O turns out to be not 90° but rather 97°, while the HSH angle is not enlarged[74].

This result can be understood as follows: Whereas the two p-AOs, namely p_x and p_y, are both involved in XH bond formation in XH_2 and are mutually orthogonal at the outset, this is no longer true for the MOs formed from a p_x or p_y and an h, since the s-AOs of the H atoms overlap. The nonorthogonality of the MOs leads to a repulsion of the H atoms and thus to a widening of the valence angle (the electrostatic repulsion of the equally charged H atoms is quite negligible compared to this "Pauli force"). The "Pauli force" varies exponentially with the distance. The separation between two H atoms in H_2O or NH_3 for a valence angle of 90° is ca. 1.4 Å and in H_2S or PH_3 is ca. 2.5 Å. It is thus clear why this force is so much weaker for the hydrides of higher row atoms than for elements of the first row and why this leads to a significant increase of the bonding angle in the latter case.

The Pauli force between the XH bonds should weaken the bonding because the HXH angle differs from that between the AOs involved in the bonding. However, a strengthening of the bonding is observed (see Section 3.1) in proceeding from OH to H_2O or from NH to NH_3 (and even to a lesser extent on proceeding from SH to H_2S or from PH to PH_3).

If hybridization is not artificially inhibited, the valence angle can be increased and the bonds simultaneously strengthened. From the population analysis presented in Figure 6, it is apparent that all the molecules discussed in this section make use of isovalent hybridization.

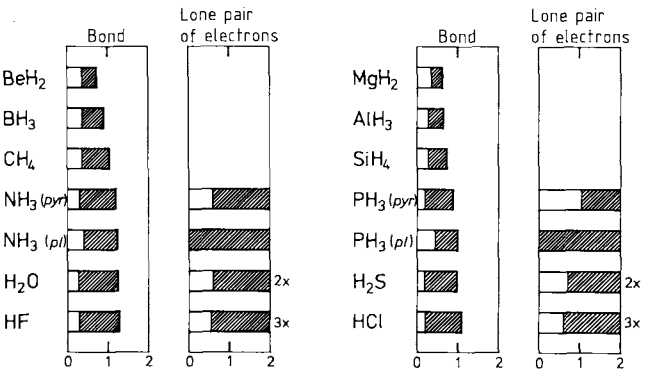

Fig. 6. Mulliken gross populations for the valence AOs of X in the localized MOs of XH_n molecules. Cf. legends to Figures 4 and 5. For NH_3 and PH_3, "pyr" signifies the pyramidal equilibrium configuration and "pl" the optimized planar structure (transition state for inversion).

In H_2O and NH_3 the s:p ratios for the hybrids forming the XH bonds are, respectively, 1:3.81 and 1:2.90. From the observed valence angles, using equation (9) one would expect ratios of 1:3.99 and 1:3.38, which is fairly consistent with the concept of orthogonal hybrids. In both of these molecules the s:p ratios for the lone pairs are, respectively, 1:2.25 and 1:2.37.

For H_2S and PH_3, s:p ratios of 1:4.71 and 1:3.83 are found for the XH bonds, whereas equation (9) yields 1:19.8 and 1:15.1 if one uses the experimental bond angles. There can thus be no suggestion of pure p bonds, nor can the lone pairs be regarded as pure 3s-AOs (s:p = 1:1.182 in H_2S and 1:0.95 in PH_3).

It is noteworthy that the hybrids for the XH bonds of OH and H_2O or SH and H_2S, etc. are not essentially different; this eliminates effect (a), shown in Figure 7 as an explanation of the varying strengths of the XH bonds in XH and XH_n. Effect (c) could at most explain why the bonds in XH_n are not weaker than those in XH. The decisive factor must clearly be effect (b).

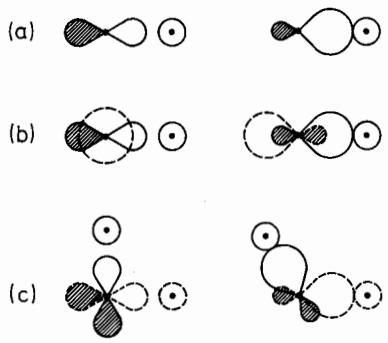

Fig. 7. Depiction of three reasons for isovalent hybridization: (a) Hybrid AOs overlap better; (b) hybridization reduces the repulsion between the XH bond and the lone pairs; (c) hybridization favors larger bond angles.

Because two OH bonds are formed in H_2O, the s→p promotion can be approximately twice as effective as in OH (the total s : p ratio for the O atom is 1 : 2, that for OH 1 : 2.23, and that for H_2O 1 : 2.70). This gives a high p component to the lone pairs, whose centroid in H_2O is displaced considerably further "outwards" from the O atom than in the OH radical. The same effect occurs (in a less pronounced way) in the comparison of H_2S with SH.

That effect (b) is actually more important than effect (c) is also apparent from the magnitude of the overlap populations which are much more strongly negative between the 2s on X and h than between h_1 and h_2. This is also supported by the observation that changes in the HXH angle for H_2O or H_2S have little effect on the valence configuration or the hybridization.

At this point two questions arise:

- Why is isovalent hybridization less used in H_2S or PH_3 than in H_2O and NH_3?
- Why are the valence angles in H_2S and PH_3 close to 90° although significantly larger HXH angles are to be expected from the valence configuration and hybridization?

One answer to the first question is that the three reasons illustrated in Figure 7 for the occurrence of isovalent hybridization in elements of the higher main groups play a less important role. The reason for this is that the 3s-AOs are much less diffuse than the 3p-AOs. Consequently, the Pauli repulsions between the XH bonds and also between the XH bond and the lone pair in H_2S are necessarily weaker than in H_2O. Finally, because of the different $\langle r \rangle_s$ and $\langle r \rangle_p$ values, the hybridization is also less effective in strengthening the bond.

The $\langle s|h \rangle$ and $\langle p|h \rangle$ overlap integrals (for p in the direction of the bond) can be extracted from the population analyses:

H_2O: $\langle s|h \rangle = 0.41$; $\langle p|h \rangle = 0.44$
H_2S: $\langle s|h \rangle = 0.33$; $\langle p|h \rangle = 0.49$

These results also confirm that the 3s-AO in H_2S is located significantly closer to the nucleus than the 3p-AO.

In view of the results obtained in Section 3.3, we should certainly not expect the valence angles calculated from s : p ratios using equation (9) to be relevant since this equation applies only to orthogonal hybrids, which are certainly not realized in H_2S. There is also one further reason for the discrepancy between the observed HSH angle and that predicted from the s : p ratio.

The actual valence angle is determined not only by the Pauli repulsion between the H atoms but also by that between the H atoms and lone pairs of electrons. The latter effect tends to favor small valence angles. When this type of repulsion is predominant, it may be said pictorially that the "lone pair needs more space than the XH bonding orbitals".

In terms of the widely used valence shell electron pair repulsion (VSEPR) model[76], the results of our analysis may be regarded as a confirmation that electron pair repulsion determines the molecular geometry. However, one weakness (among others[74]) of this model is that it completely ignores the role of hybridization in assuming ideal hybridization is always realized[77].

Since comparison of NH_3 with PH_3 leads to a completely analogous result as that of H_2O with H_2S, we need not repeat the same arguments here. It is worthwhile, however, to comment on the analysis of planar NH_3 and PH_3 (cf. Fig. 6). In this instance, the lone pair is necessarily of π type, i.e. a pure p-AO, and one might expect (similarly as in BH_3 or AlH_3) that the sp^2 hybridization for the XH bonds is "enforced". It is found, however, that the s : p ratio for X in the XH bonds in NH_3 and PH_3 is only 1 : 1.5 and 1 : 1.25, respectively.

The inversion barrier for NH_3 is 6 kcal/mol and that for PH_3 around 38 kcal/mol[78]. This enormous difference (cf. Fig. 6) arises because the valence configuration of NH_3 has to change only from $s^{1.53}p^{4.11}d^{0.03}$ to $s^{1.41}p^{4.26}d^{0.01}$ from the equilibrium to the planar structure; in contrast, PH_3 has to change from $s^{1.59}p^{3.04}d^{0.12}$ to $s^{1.32}p^{3.62}d^{0.09}$.

It is not only the strong s→p promotion which requires energy. In planar PH_3 the lone pair is necessarily a 3p-AO which functions better as a valence AO than as a lone pair.

3.7. Comparison of CH_2 with SiH_2, GeH_2, and SnH_2

In its ground configuration s^2p^2, C — like Si, Ge, etc. — is bivalent; accordingly CH_2, SiH_2, GeH_2, etc. in the $^1A_1$ states require no promotion. Population analyses (Fig. 8) and HXH angles[78–80] (CH_2 102.4°, SiH_2 94°, and GeH_2 92°) confirm that in CH_2 as in H_2O or NH_3 use is made of isovalent hybridization (s : p = 1 : 1.56), whereas SiH_2 corresponds rather to H_2S (s : p = 1 : 1.04).

In contrast, formal promotion into the sp^3 valence configuration is necessary for formation of the $^3B_1$ states, since two valence AOs are needed for each XH bond and two further AOs for unpaired electrons. The HXH angles[79–81] are correspondingly considerably larger (CH_2 136°, SiH_2 117.6°, and GeH_2 118.6°), although the s : p ratios deviate markedly from 1 : 3 (CH_2 1 : 2.11 and SiH_2 1 : 1.77).

The assumption of orthogonal hybrids is not justified in all cases. From the degree of hybridization one would expect significantly larger valence angles, especially in SiH_2 but also in CH_2. Admittedly, the potential curves as a function of angle are very flat, particularly for $CH_2(^3B_1)$.

Alternatively, one can interpret the HXH angles in XH_2 molecules using Walsh diagrams[82].

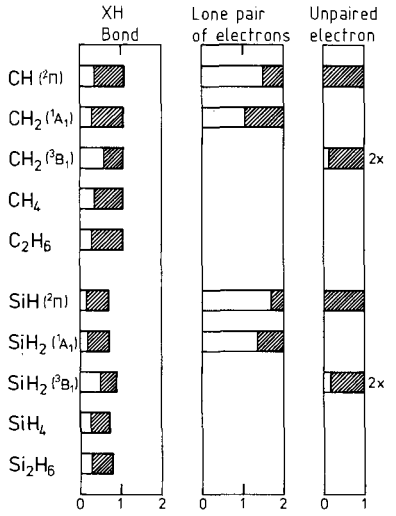

Fig. 8. Mulliken gross populations for the valence AOs of X in the localized MOs of XH_n molecules (X=C, Si). Cf. legends to Figures 4 and 5.

In the series CH_2, SiH_2, GeH_2, SnH_2, the only molecule with a triplet ground state is CH_2. This suggests that the promotion energy for hybridization required for the formation of the $^3B_1$ states is over-compensated by the gain in bond energy only for the C atom.

The effect of substituents on the geometry of XH_2 species and on the singlet-triplet state separation cannot be treated here[80,83].

3.8. Monofluorides and "Saturated" Fluorides

The bonding energies of XF bonds are illustrated in Figure 9. There is a pronounced maximum in the curve for elements of the third main group (B to Tl).

The monofluorides of elements of the first row have stronger XF bonds than the "saturated" polyfluorides; the bond in BF is ca. 30 kcal/mol stronger than a BF bond in BF_3. This trend is also apparent in a less pronounced form in the second row for AlF/AlF_3, whereas the SiF bond in SiF is weaker than that in SiF_4.

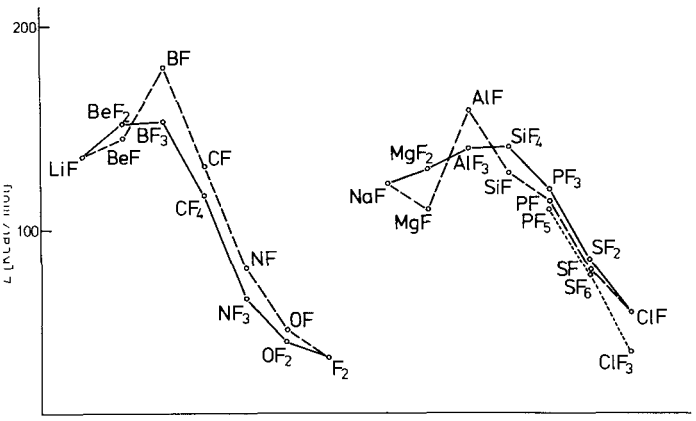

Fig. 9. XF bond energies in monofluorides XF and XF_n molecules (for the sources of these values see Appendix 1).

The extraordinary strength of the bond in BF undoubtedly arises because this compound is isoelectronic with CO and N_2, and some remnant of a triple bond is present. In addition to the σ-bonding in the BF molecule, there is also π-backbonding, although this is much less pronounced than in N_2 or CO since charge has to be displaced from F to B, i.e. against the difference in electronegativity. (In CO only one of the two π-bonds is due to backbonding, whereas in N_2 both are true covalent bonds.) Stabilization of the BF bonds by backbonding is also possible in BF_3 (where the pπ-AO of the B atom is formally unoccupied), but not in CF_4. The high strength of the XF bonds in CF, BF, and OF can be rationalized in a similar way.

The marked difference between the bonds in CF and SiF probably arises, on the one hand, because the π-type backbonding in SiF is much weaker than that in CF (cf. Section 4.1) and, on the other hand, because of possible stabilization even of the SiF_4 by backbonding with the involvement of d-AOs on the Si (cf. Section 5.3). The greater polarity of the SiF bond also plays a role.

The bond lengths[69] (which are not discussed here) tend to support this overall picture. Thus, when X is from the first row, the SF distances increase by ca. 0.03—0.04 Å in going from the monofluorides XF to the saturated, normal-valent polyfluorides XF_n, whereas when X is from the second row, a corresponding shortening of 0.01 to 0.03 Å occurs.

In Figure 9 a number of hypervalent molecules, namely PF_5, SF_6, and ClF_3 (see Section 5.2) are included. The bond energy per XF bond is always smaller in the hypervalent fluorides than in the saturated fluorides, as is apparent from a comparison of PF_5 with PF_3 or of ClF_3 with ClF.

The differences between XH_n and XF_n molecules depend, in part, on the high polarity of the XF bonds and also to an extent on the fact that there are occupied π-electron orbitals on F which permit backbonding.

4. Multiple Bonds in Light and Heavy Main Group Elements

4.1. Bonding Increments

The bond energies for homonuclear diatomic molecules are collated in Figure 10. In going from the first to higher homologous rows, there is a very evident decrease in the bond energies (with the sole exception of F_2 which has a smaller bond energy than Cl_2).

Bond energies of molecules (especially those in which all the bonds are highly localized) can be resolved into (approximately transferable) contributions from the individual bonds. Accordingly, it is entirely reasonable to speak of the energy of a CC single bond or of a CC double bond. Of course, if one wishes to determine the energies in given molecules very accurately by means of an increment system, (transferable) contributions for each of the individual bonds are not sufficient. Then additional increments for interactions, ring strains, etc. are also required[84]. However, we are not concerned here with an increment system which may be used to reproduce any given bond energy, but rather in rationalizing our knowledge of empirical in-

formation on bond energies between main group atoms in a simple and concise way.

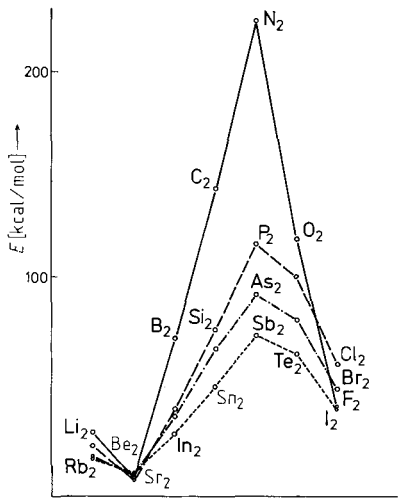

Fig. 10. Bond energies for homonuclear diatomic molecules (for the sources of these values see Appendix 1).

Instead of documenting the energies for single, double, and triple bonds, we resolve them into σ and π contributions (following *Pauling*[129]) and list these in Table 2. This resolution is, to a certain extent, entirely arbitrary. We have, for example, simply identified the CC σ-increment with the energy of a CC single bond (cf. Appendix 2) (the atomization energy of C_2H_6 has been used, with the assumptions that the bond energy of a CH bond in C_2H_6 is the same as that in CH_4 and that non-neighboring interactions or multicenter effects can be ignored). The CC π-increment is then simply the difference between the energy of the CC double bond in ethene and that of the CC single bond in ethane (cf. Appendix 2). No account has been taken of the fact that the σ-bond in ethene is certainly different from that in ethane.

Table 2. Bond increments (in kcal/mol) for σ/π-bonds [a].

CC	NN	OO	FF	CN	CO	NO
80/70	38/94	35/83	37/—	70/65	80/90	45/88
SiSi	PP	SS	ClCl	SiC	PC	SC
46/28	48/34	64/37	58/—	72/33	64/48	67/63
GeGe	AsAs	SeSe	BrBr	SiO	PO	SO
39/26	42/29	50/30	45/—	100/40	80/36	65/60

[a] The sources of these values are cited in Appendix 2.

Table 2 indicates that the π-increments for homonuclear bonds involving first row elements (C to O) are more than twice as large as those involving second row elements. Elements of the second and higher rows differ only little. For the higher rows the σ-increments are significantly larger than the π-increments, exactly the opposite of that found for the first row, namely for N and O (even the small FF σ-increment fits into this pattern). The CC bond is somewhat exceptional in that the σ- and π-increments are of roughly the same magnitude.

These increments reflect that, in general, compounds having OO or NN single bonds are very unstable, and that normally O and N exhibit multiple bonds and exist as O_2 and N_2. Moreover, SiSi, PP, or SS multiple bonds are usually less favored than the corresponding single bonds, and for silicon, phosphorus, and sulfur, structures having single bonds only are preferred.

The enormous variety of organic chemistry is largely due to the fact that CC σ- and π-bonds are competitive with each other. Although the σ-bonds are somewhat stronger—which is why it is justified to speak of molecules with double bonds as "unsaturated"—π-bonds can be stabilized by delocalization. Thus, aromatic molecules are just about as stable as aliphatic molecules, and the cohesive energies of graphite and diamond are virtually identical.

Such a competition between σ- and π-bonds is unique in the periodic system of the elements, notwithstanding recent work[10,11] in which SiSi double bonds have been prepared. Molecules of this type (completely in accord with the increment system in Table 2) are either short-lived or are "kinetically stabilized" by appropriate substitution to prevent oligomerization reactions.

For bonds formed between different atoms, one finds that the π-bonds are stronger when both atoms are from the first row (N-O) or that the σ-bonds or are of comparable strength (C—N, C—O). The NO bond thus behaves analogously to the NN and OO bonds, whereas CN and CO behave like CC bonds, so that the special role of the carbon tends to dominate.

When at least one atom is from the second or a higher row, the σ-increments are much larger than the π-increments—with the exceptions of CS (and possibly also CSe) and SO, for which the σ- and π-increments are comparable.

Single and multiple bonds compete not only in CC bonds but also in CN, CO and CS bonds, which is certainly related to the special role played by nitrogen, oxygen, and sulfur in organic chemistry.

An appropriate measure for the different strengths of π-bonds is also provided by the shortening of the atomic distances in proceeding from single to double bonds (ca. 12% in C, 9% in Si[85a] and 0% in Sn[85b]).

4.2. Electronic Structure of Homonuclear Diatomic Molecules

To understand the notable pattern of the σ- and π-increments (cf. Section 4.1), we consider the overlap of 2pσ- and 2pπ-AOs as a function of the distance between the two atoms (Fig. 11). In view of this overlap it has to be expected that σ-bonds are stronger than π-bonds, at least for distances that are not too small. Elements of the higher rows display in this sense the normal behavior, while those in the first row would represent exceptions.

How is it possible for first row elements to have π-increments which are larger than their σ-counterparts? The key to understanding this surprising result is again found in the relative spatial distributions of the 2s- and 2p-AOs compared to those of the 3s- and 3p-AOs. This type of argument has already been used in Section 3.6 to account for the different geometries of H_2O and NH_3, on the one hand, and H_2S and PH_3, on the other. The relevant mechanism is presented in many textbooks of theoretical chemis-

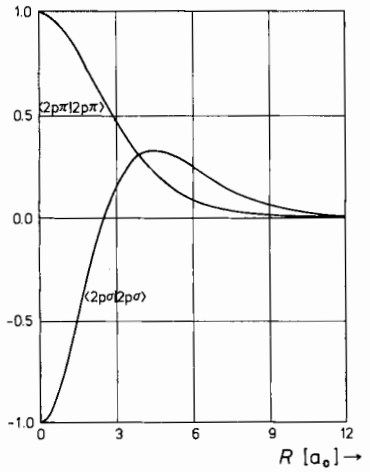

Fig. 11. A comparison of the 2pσ and 2pπ overlap integrals as a function of the distance between the two atoms.

try[86] in the context of the electronic structure of diatomic homonuclear molecules (Fig. 12). If the MOs were constructed from the "pure" 2s- and 2p-AOs of the atoms, the sequence of valence MOs would then be: $2\sigma_g$, $2\sigma_u$, $3\sigma_g$, $1\pi_u$, $1\pi_g$, $3\sigma_u$, where the first two MOs originate from 2s and the last four from 2p orbitals. As a consequence of the interaction of the 2s and 2p orbitals, the energies of MOs of the same symmetry will be shifted away from each other such that the following sequence results: $2\sigma_g$, $2\sigma_u$, $1\pi_u$, $3\sigma_g$, $1\pi_g$, $3\sigma_u$.

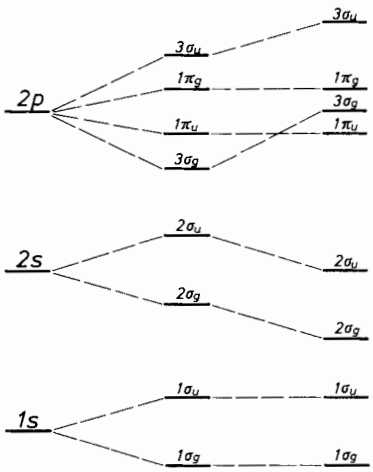

Fig. 12. Schematic representation of the MO levels in homonuclear diatomic molecules.

According to the Aufbau principle, the $1\pi_u$-MO is initially doubly occupied in B_2 and quadruply occupied in C_2 before the $3\sigma_g$-MO is occupied in N_2. Hence, B_2 has a π-bond, C_2 two π-bonds, and N_2 two π-bonds and a single σ-bond.

4.3. Comparison of N_2 with P_2

Since the "mixing" between the s and p valence AOs is less effective for the higher row elements—owing to the greater spatial separation of s and p—than that for first row elements, we would expect the displacement of the levels corresponding to the $2\sigma_g$ and $3\sigma_g$ levels in P_2, for example, to be smaller than that in N_2. This is confirmed by comparing the one-electron energies in the potentials for $N_2^{6\oplus}$ and $P_2^{6\oplus}$ (where the MOs formed mainly from s valence AOs are fully occupied): As shown in Figure 13, the $3\sigma_g$ level in N_2 lies above the $1\pi_u$ and the $5\sigma_g$ level in P_2 is found below the $2\pi_u$, even though in both instances the difference in energy is not very large, namely of the order of 1 eV. It is also found experimentally[87] that the first ionization potential for N_2 corresponds to ionization from the $3\sigma_g$ level (which should thus be the highest occupied MO) and for P_2 to ionization from the $2\pi_u$[88] level.

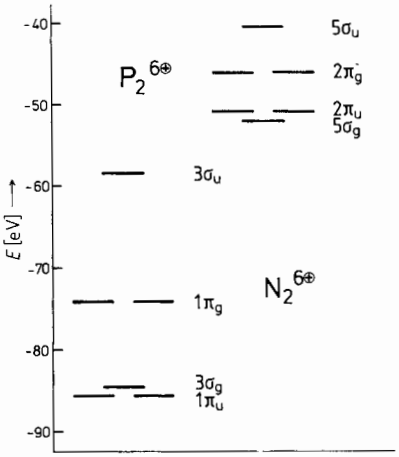

Fig. 13. Energy levels in the field of $N_2^{6\oplus}$ and $P_2^{6\oplus}$.

The MO arguments upon which Figure 13 is based can also be translated into the terminology of hybridization. Thus the nitrogen atom N, for example, is tervalent in its ground configuration $1s^2 2s^2 2p^3$ and can thus form an N_2 molecule with a triple bond. The bond is weakened by Pauli repulsion between the doubly occupied 2s-AOs and between the σ-bond and either of the doubly occupied 2s-AOs. These repulsions can be attenuated by isovalent hybridization, in an extreme model by promotion to the valence configuration $1s^2 di^3 2p^2 = 1s^2 2s^{1.5} 2p^{3.5}$, where di represents a digonal or sp hybrid AO as in equation (13). In this context, di^3 signifies that of the two hybrid AOs di_1 and di_2 one is doubly occupied with a lone pair while the other is available as a valence AO for the NN bond. Isovalent hybridization of this type reduces the Pauli repulsion and also strengthens the NN σ-bond (see Fig. 7), but costs promotion energy. Both of these effects should be less pronounced in P_2, where from the outset the Pauli repulsion is less important.

The valence configuration for N_2 is $s^{1.77} p^{3.17} d^{0.06}$ and that for P_2, $s^{1.82}$, $p^{3.09} d^{0.09}$; the valence configuration in P_2 thus lies rather closer to the ground configuration $s^2 p^3$ (implying less promotion energy), although even for N_2 it is still sufficiently far away from the configuration required for the formation of digonal hybrids, namely $s^{1.5} p^{3.5}$.

The s and p populations for individual MOs are given in Figure 14. The mixing of p into the $4\sigma_g$ and $4\sigma_u$ levels is smaller for P_2 than it is into the $2\sigma_g$ and $2\sigma_u$ levels in N_2. The same holds for the mixing of s into the $3\sigma_g$ or $5\sigma_g$ levels.

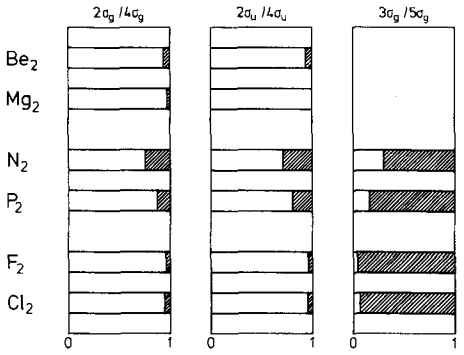

Fig. 14. Mulliken gross populations for the s and p valence AOs in the canonical MOs of X_2 molecules. In each case from left to right: s, p (hatched). The AO bases used are as in Figure 4.

The σ-bonds in N_2 and P_2 lie between pure p-bonds and sp hybrid bonds; they are closer to pure p-bonds, especially in P_2.

Mulliken and *Liu*[90] were the first to point out the role of the different isovalent hybridization. The difference is, however, too small to explain the enormous differences in the σ- and π-increments. Further insight is gained from the overlap populations. The total overlap populations for the XX bond are

N_2: 0.71 P_2: 0.73

and these may be resolved into the following σ and π contributions

N_2, σ:	0.17	P_2, σ:	0.23
π:	0.27	π:	0.25

where "π" indicates the contribution for either of the two π-bonds. The σ-bond in N_2 is evidently weaker than a π-bond, whereas in P_2 both types of bonds should have roughly the same strength. The σ overlap populations can be further resolved into the contributions from the ss, spσ, and pσpσ (and additionally sdσ, pσdσ, dσdσ) overlaps:

N_2 ss:	−0.13	P_2 ss:	−0.04
spσ:	0.05	spσ:	0.00
pσpσ:	0.10	pσpσ:	0.16

The relative weakness of the σ-bond in N_2 clearly results from the negative ss overlap population, i.e. from the repulsion of the 2s-AOs. This is attenuated to some extent by isovalent hybridization, i.e. the repulsion would be even stronger if the lone pairs were frozen-in as pure 2s-AOs. The 3s-repulsion in P_2 is substantially weaker.

Alternatively, the total σ-overlap populations can be resolved into $2\sigma_g$, $2\sigma_u$, and $3\sigma_g$ contributions for N_2 and $4\sigma_g$, $4\sigma_u$, and $5\sigma_g$ contributions for P_2

N_2 $2\sigma_g$:	0.40	P_2 $4\sigma_g$:	0.32
$2\sigma_u$:	−0.19	$4\sigma_u$:	−0.09
$3\sigma_g$:	−0.04	$5\sigma_g$:	0.00

According to this scheme, $2\sigma_g$ or $4\sigma_g$ is strongly bonding, $2\sigma_u$ or $4\sigma_u$ is weakly antibonding, and $3\sigma_g$ or $5\sigma_g$ virtually nonbonding.

On the basis of only the total overlap populations, it might perhaps be expected that the triple bonds in N_2 and P_2 are approximately equal in strength.

However, it is not justified to relate the overlap populations directly to bond energies. The bond energy is also determined by how strongly valence electrons are attached to the core of the free atom, i.e. essentially by the ionization potential. This is larger for p-AOs in N than in P by a factor of 1.3. If the greater s contribution to valence in N is taken into account, the factor should be even slightly larger. Thus, in qualitative terms at least, it is clear why the bond energy in N_2 is significantly greater than that in P_2.

4.4. Comparison of Be_2 with Mg_2

We have seen for N_2 and P_2 that the $2\sigma_g$- or $4\sigma_g$-MOs are strongly bonding, whereas the $2\sigma_u$- or $4\sigma_u$-MOs are weakly antibonding (Section 4.3). If this were true for all X_2 molecules, Be_2 and Mg_2 should be stable molecules.

The Mg_2 molecule has been detected experimentally[91] (equilibrium separation $r_e = 3.89$ Å, bond energy $D_e = 1.2$ kcal/mol). The Be_2 molecule is known only from—albeit very reliable—quantum-chemical calculations[92,93], according to which it should have $r_e = 2.50$ Å and $D_e = 2.0$ kcal/mol, i.e. it should have a stronger bond than that in Mg_2. The Ca_2 molecule has an even stronger bond than Be_2 or Mg_2. The equilibrium separation and bond energy for Mg_2 suggest the presence of a van der Waals' bond, such as occurs between any closed shell systems (e.g. He_2: $r_e = 2.97$ Å, $D_e = 0.02$ kcal/mol; Ne_2: $r_e = 3.07$ Å, $D_e = 0.05$ kcal/mol). In contrast to chemical bonds, the van der Waals' bond (cf. [94]) does not arise from the overlap of orbitals but from the mutual induction of transient dipoles. It can be shown that such a bond will be stronger the greater the dipole polarizability between the atoms or molecules involved. Mg_2 has a very high dipole polarizability (cf. Table 1), which explains why the bonding is much stronger than that in He_2 or Ne_2. From the trend in dipole moments (Table 1), one might expect that the bond strengths should decrease along the sequence Ca_2, Mg_2, Be_2. As already mentioned, however, Be_2 is probably more strongly bound than Mg_2 (in accord with the higher cohesive energy of solid Be compared to solid Mg).

SCF calculations predict that neither Be_2 nor Mg_2 are bound, and not even local minima are found on the potential energy curves. To obtain reliable predictions, one has to treat electron correlation effects[96] in a highly sophisticated manner[92,93]. Nevertheless, even the potential curves obtained from SCF calculations are peculiar.

Whereas strong overlap of atomic orbitals normally results in either marked repulsion or attraction (chemical bonding), for Be_2 in particular (and to a lesser extent Mg_2) one finds only a very weak repulsion when there is strong

overlap. This is because the bonding effect of the $2\sigma_g$ and the antibonding effect of the $2\sigma_u$ largely compensate each other. Normally, an antibonding MO is always much more strongly antibonding than the corresponding bonding MO is bonding. The mixing in of p components into these MOs (cf. Fig. 14) strengthens the bonding character of the $2\sigma_g$ and reduces the antibonding of $2\sigma_u$. It is plausible that this effect is not as pronounced as in N_2, since in the N atom the $2p\sigma$ is occupied but is not in the Be atom.

The bonding in Be_2 is stronger than in Mg_2 because the hybridization of first row elements is more effective than that of higher row elements. Be_2 obviously represents a borderline case between (weak) chemical bonding and (strong) van der Waals' bonding.

One of the strongest genuine van der Waals' bonds occurs in the lowest triplet state of Li_2 ($r_e = 4.2$ Å, $D_e = 0.8$ kcal/mol[95]). This is more comparable with the bond in Mg_2 than that in Be_2. If there were a genuine van der Waals' bond in Be_2, this bond should be substantially weaker than that in the Li_2 triplet because the polarizability of Li (Table 1) is approximately four times that of Be.

4.5. Explanation of the Different σ- and π-Increments

In principle, the σ-bond increments (cf. Appendix 2) have been derived from the molecules C_2H_6, N_2H_4, H_2O_2, F_2, Si_2H_6, P_2H_4, H_2S_2, and Cl_2 assuming that the respective XH bonds are the same as those in CH_4, NH_3, H_2O, SiH_4, PH_3, and H_2S. A comparison of the results of population analyses in Figures 15 and 6 reveals that this assumption is reasonable—at least as far as the s : p ratios for the AOs of X in XH bonds are concerned. The hybridization of the lone pairs in the corresponding molecules also appears to be remarkably similar, even for HF and F_2 or HCl and Cl_2.

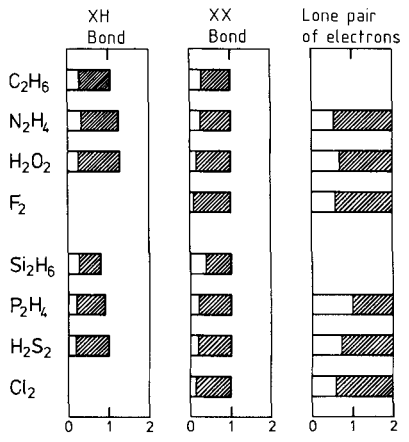

Fig. 15. Mulliken gross populations for the s and p valence AOs of X in the localized MOs of X_2H_{2n} molecules. Cf. legends to Figures 4 and 5.

In addition to Pauli repulsions between pairs of XH bonds and between XH bonds and lone pairs, which we encountered in our discussion of XH_n molecules, there exists in X_2H_{2n} molecules a repulsion between the lone pairs of the two X atoms, as discussed for X_2 molecules (Sections 4.2 and 4.3). While the first two repulsions can be reduced by isovalent hybridization, for the last-mentioned repulsion hybridization is rather less effective (as the comparison of NH_3/N_2 showed). Accordingly, the XX bonds in N_2H_4, H_2O_2 and F_2 are approximately pure p bonds, whereas mixing with s components is more pronounced in the XH bonds.

If the contributions to the XX overlap population from the localized MOs in the XX bond are compared (Table 3) in the series C_2H_6, N_2H_4, H_2O_2, F_2, a smooth variation is observed without any jump between C_2H_6 and N_2H_4. There is a jump, however, in the contributions of the remaining localized MOs to the XX overlap population. The repulsion of the CH bonds in C_2H_6 thus only slightly weakens the CC bond, whereas the repulsion of the lone pairs in N_2H_4, H_2O_2, and F_2 causes substantial weakening of the bond. This weakening is apparently responsible for the jump in the total σ-bond increments in proceeding from C_2H_6 to N_2H_4 (cf. Table 2). Nevertheless, some peculiarities are not easily understood. Why is the weakening of the XX bond through lone-pair repulsion almost the same for N_2H_4, H_2O_2, and F_2 although the number of lone pairs per X is 1, 2, and 3, respectively? A possible explanation is that a bond lengthening from N_2H_4 to F_2 occurs as a result of the lone-pair repulsion and that the net repulsion decreases with the bond length. Furthermore, the empirical σ-increments in Table 2 hardly change in going from NN via OO to FF, whereas the total overlap populations (Table 3) in this series show a distinct decrease. This certainly arises in part (as already discussed in Section 4.3 for the comparison of N_2/P_2) because the bond energy is determined not only by the overlap population but also by the ionization potential of X. The latter increases from N to F and to some extent compensates for the reduction in the overlap population. The fact that the SCF approximation upon which our population analyses have been based becomes increasingly poor along the series $C_2H_6 \ldots F_2$ may also play a role. The effects of electron correlation[96] in this series become increasingly important and lead to a strengthening of the bonding that is not reflected in the population analyses (based on SCF calculations).

Table 3. Mulliken XX overlap populations for X_2H_{2n}-molecules [a].

	C_2H_6	N_2H_4	H_2O_2	F_2
LMO for the XX bond	0.43	0.40	0.30	0.25
Remaining MOs	−0.05	−0.23	−0.22	−0.21
Total	0.38	0.17	0.08	0.04
	Si_2H_6	P_2H_4	H_2S_2	Cl_2
LMO for the XX bond	0.46	0.41	0.36	0.31
Remaining MOs	−0.06	−0.12	−0.16	−0.23
Total	0.40	0.29	0.20	0.08

[a] Cf. Fig. 15.

Let us now compare the X_2H_{2n} molecules of the first with those of the second row! The XX overlap populations arising from the localized MOs for the XX bonds are only slightly larger in the series Si_2H_6, P_2H_4, H_2S_2, Cl_2 (Table 3) than in the series $C_2H_6 \ldots F_2$. In contrast, the contributions of the remaining localized MOs to the total X overlap population, especially in P_2H_4 and H_2S_2, are quite different from the corresponding values for N_2H_4 and H_2S_2. This

confirms the reduced importance of lone-pair repulsion for the elements of the higher rows.

The total XX overlap populations illustrate why the σ-increments for the second row elements are greater than those for first row elements, particularly in comparing NN and OO with PP and SS, although, in general, second row atoms tend to form stronger bonds (cf. Figs. 3 and 10). The change in the overlap populations in going from H_2O_2 to H_2S_2 is so great that the variation in ionization potential from O to S—which operates in the opposite sense—is insufficient to reverse the trend.

Interestingly, the NN σ-overlap population in N_2H_2 (0.17) is almost the same as that in N_2 (0.17) (despite the different bond lengths), whereas in P_2H_4 it is rather larger (0.29) than in P_2 (0.23).

Notwithstanding the significant weakening of the XX bond for X = N or O by the repulsion of the lone pairs, the XX multiple bonds are stronger than for X = P, As or S, Se (cf. Fig. 10). This principally occurs because the valence electrons are bonded—even in the isolated atoms—more strongly in first row than in higher row atoms (cf. Section 4.3 and Fig. 1). Since the lone pair repulsion is included entirely in the σ-increments, the π-increments for the first row are accordingly larger than those for the higher rows.

4.6. Comparison of P_4 with P_8; Ring Strain in Phosphorus Rings

In view of the different σ- and π-bond increments for N and O, on the one hand, and P, S, and As, Se, etc., on the other, it is hardly surprising that the most stable allotropes of nitrogen and oxygen are N_2 and O_2 molecules, respectively, whereas for phosphorus and sulfur larger molecules (e.g. P_4, S_8) having only single bonds are preferred. The relative stability of the P_4 tetrahedron is nevertheless, surprising, for—as in tetrahedrane—considerable ring strain might be expected. Comparison of the atomization energy of P_4 (284 kcal/mol) with six times the PP σ-increment ($6 \times 48 = 288$ kcal/mol) indicates the absence of strain energy. The same conclusion is reached by comparing the thermochemical data for the isodesmic reaction $P_4 + 8\,PH_3 \rightarrow 6\,P_2H_4$ in which the number of PH bonds and PP bonds is maintained. According to calculations carried out by *Schoeller* and *Staemler*[98a], also cyclic $(PH)_3$ exhibits practically no strain energy. The corresponding strain energy in tetrahedrane is, however, 122 kcal/mol[97] and that of cyclopropane, 25 kcal/mol[98b,c].

It should not immediately be concluded that the absence of strain energy implies the absence of ring strain, since the reference energy of the PP single bond in P_2H_4 is already weakened (by repulsion of the lone pairs), even if the same repulsion is also present in P_4 and in $(PH)_3$. It is also rather surprising that a cubic P_8 species is unknown; this would also have only PP single bonds, and the valence angles would be very close to the optimal value for P of 92—94°, which should be more propitious than the tetrahedral angle.

Ab initio pseudopotential calculations[99,100] provide some useful insight[99] in comparing the molecules X_2, X_4, and X_8 (X = N, P, and As). As might be expected, the hypothetical N_4 species has a substantially higher energy than that of $2\,N_2$ (by more than 200 kcal/mol), whereas P_4 lies either close to or slightly below $2\,P_2$ in energy, depending on the level of sophistication of the calculation. The As_4 species is always well below $2\,As_2$ in energy. For P_4 the inclusion of d-AOs is decisive for the stabilization of P_4 with respect to $2\,P_2$, although the relative lowering of the energy by the dAOs amounts to only ca. 30 kcal/mol with a d-AO population of 0.10 in P_4 and 0.06 in P_2 (very similar values are found for N_2/N_4 and As_2/As_4). The role played by the d-AOs here is thus of much less importance than for hypervalent P compounds (cf. Sections 5 and 6), although it is certainly not insignificant. The conclusion reached in earlier work[101a] that the PE spectrum of P_4 can be accurately reproduced even without d-AOs—and that as a consequence the d-AOs are not important—was thus undoubtedly premature.

A calculation without d-AOs indicates that cubic P_8 is more stable than $2\,P_4$ by ca. 10 kcal/mol. Although *Trinquier* et al.[99] were not able to perform a calculation on P_8 with d-AOs, they argued persuasively that the contribution of d-AOs in cubic P_8 should be substantially smaller than that in tetrahedral P_4, with the result that with d-AOs P_8 should not be stable compared to $2\,P_4$. These authors also argue plausibly that parallel PP bonds repel each other and that this repulsion is more important than the ring strain in P_4.

Even though the precise relative energetic position of P_8 with respect to $2\,P_4$ is not known, it can be demonstrated by symmetry considerations similar to the Woodward-Hoffmann rules that the $P_8 \rightarrow 2\,P_4$ reaction is thermally forbidden[101b]. Accordingly, P_8 should not rearrange into $2\,P_4$ or vice versa, at least not unimolecularly. What is more likely to occur is a polymerization of P_8 to black phosphorus in which only a few of the bonds would have to "jump" and the valence angles would need to be increased only by a small amount. The possibility of such a polymerization has yet not been investigated theoretically, and it is not known whether cubic P_8 represents at least a local minimum in the potential hypersurface for the P_8 system.

Similarly, in black phosphorus only PP single bonds with evidently optimal valence angles occur, without any repulsion of parallel PP bonds. Presumably, there is also a metallic (delocalized) bonding contribution which has the effect that the cohesive energy per PP bond of 53 kcal/mol is considerably greater than the PP σ-increment (48 kcal/mol).

4.7. SiC and SiO Double Bonds

The SiC double bond resembles the SiO double bond in that it is less favored energetically than two SiC single bonds. From the bond energy increments we obtain ca. 78 kcal/mol for the dimerization energy of H_2SiCH_2 to the cyclic dimer (with an Si—C—Si—C ring), provided that the strain energy—which is not expected to be large—is neglected. On the basis of an ab initio calculation, *Ahlrichs* and *Heinzmann*[102] obtained a reaction energy of ca. 76 kcal/mol for this process. What is perhaps more interesting is that they found a barrier of only ca. 4 kcal/mol,

which suggests that the thermal dimerization is no longer symmetry—forbidden, unlike that of ethene.

Although the SiC bond is substantially polar, the SiO bond in e.g. oxosilane H_2SiO is even more polar. In fact, it is so polar that a description in terms of a semipolar bond $H_2Si^{\oplus}-O^{\ominus}$ approaches the real situation rather better than the traditional formulation with a double bond $H_2Si=O$[103]. This bond actually has a number of similarities to the genuine semipolar bond, in $H_3P^{\oplus}-O^{\ominus}$. There is even a similar d-AO population on the silicon atom in H_2SiO as that on the phosphorus atom in H_3PO[104] (0.2 and 0.3 electrons, repectively).

5. Molecules which Apparently Violate the Octet Rule

5.1. Hybrids with d-Involvement or Multicenter Bonds?

A significant difference in the chemistry of elements of the first and higher rows is the appearance of compounds such as SF_6, XeF_2, XeF_6, etc. which seem to violate the octet rule.

To describe the bonding in these molecules, two different models have been proposed[104b]:

(a) The involvement of d-AOs leading, for example, to sp^3d^2 hybrids[29,55].
(b) The formation of three-center, four-electron bonds without any significant d-AO contribution[105].

The formation of a three-center, four-electron bond is depicted in the lower part of Figure 16. In XeF_2, for example, three MOs can be constructed as linear combinations of the pσ valence AOs of the Xe on the two F atoms. Of the three MOs, one is bonding (σ_b), one nonbonding (σ_n), and one antibonding (σ_a) (the dσ-AO at σ_n drawn with dashed lines (cf. Fig. 16) should be ignored). Four electrons (two from the Xe and one each from the two F atoms) occupy the σ_b and σ_n MOs, so that overall bonding will occur[106].

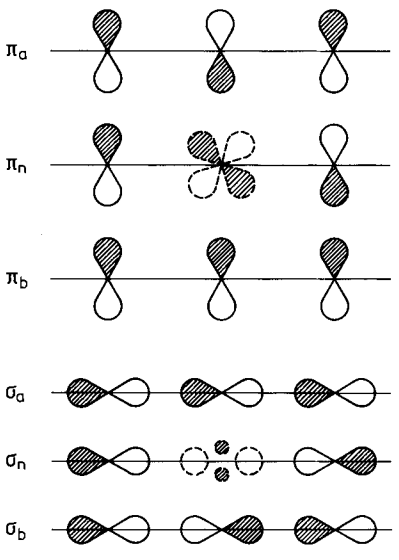

Fig. 16. MOs for a three-center, four-electron σ-bond (lower part of figure) and for backbonding (upper part of figure). The d-AOs not absolutely essential for this bond but which can reinforce it are sketched with broken lines.

The counterpart of this three-center, four-electron bond in VB theory would be mesomerism between two ionic structures

$$F^{\ominus}\cdots Xe^{\oplus}-F \longleftrightarrow F-Xe^{\oplus}\cdots F^{\ominus}$$

This formulation illustrates (as does the MO picture) that each of the F atoms bears approximately half a negative charge and that each XeF bond has a covalent and an ionic component. This bonding situation is favored[106,107] if the central atom (in this case Xe) has a small ionization potential and the outer atom (in this case F) is as electronegative as possible.

When d-AOs on the central atom (dashed lines in Fig. 16) are available for bonding, the σ_n MO can also become bonding, which has the overall effect of stabilizing the bond. In the hypothetical case that both pσ and dσ valence AOs on Xe were equally occupied, it would then be possible to speak of pd-hybrids.

5.2. Comparison of NH_3F_2 with PH_3F_2

It is instructive to compare the hypothetical molecule NH_3F_2 with the known[108] molecule PH_3F_2. This should enable us to understand the different behavior of N and P as respective representatives of the first and higher rows[109].

Both of these molecules may formally be constructed from a planar XH_3 unit and two F atoms such that the π-type lone pair on the XH_3 (similarly to the pσ-AO on Xe) forms a three-center, four-electron bond with the two p-AOs from the F atoms. If our conception of the role of the ionization potential for the central atom is correct, we should expect that an FXF bond is formed in both molecules, since both planar PH_3 and planar NH_3 have ionization potentials (9.9 and 10.9 eV, respectively) lower than that e.g. of Xe (12.10 eV). In fact, in the symmetric D_{3h} configuration (cf. Fig. 17) both PH_3F_2 and NH_3F_2 are stable with respect to planar XH_3 and an F_2 molecule[109].

For NH_3F_2 the stabilization is, however, only a few kcal/mol, whereas for PH_3F_2 it is 170 kcal/mol. The contribution of the d-AOs on the X atom to the bond energy has already been taken into account here (for NH_3F_2 ca. 7 kcal/mol, and for PH_3F_2 ca. 40 kcal/mol).

In this respect there is a clearcut quantitative difference between NH_3F_2 and PH_3F_2 but no qualitative difference. Qualitatively the two molecules behave differently with respect to a lowering of the symmetry from D_{3h} to C_{3v} (cf. Fig. 17). Although the potential hypersurface for PH_3F_2 does indeed have its minimum for D_{3h} symmetry, the energy of NH_3F_2 is lowered if the symmetry is reduced to C_{3v}. The most stable C_{3v} structure corresponds essentially to the ion pair $H_3NF^{\oplus}\cdots F^{\ominus}$[110]. The calculated values of the NF separation and the HNF bond angle in the $NH_3F^{\oplus}$ moiety are 1.41 Å and 107°, respectively, and for the other NF distance 2.06 Å. The NF bonds in the optimal D_{3h} structure appear to be unusually long at 1.70 Å, much too long for covalent NF bonds, which explains why the bonds

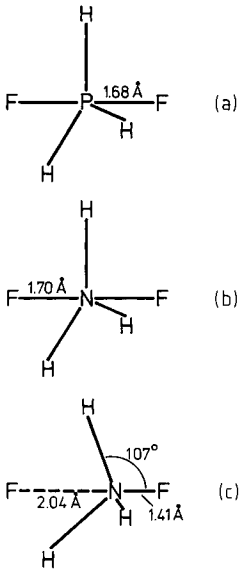

Fig. 17. Geometric structures of PH_3F_2 and NH_3F_2: (a) and (b) with D_{3h} symmetry; (c) lowering of symmetry to C_{3v}.

are only very weak. It is therefore much more favorable if one F atom is covalently bonded (at the normal distance) and the other F atom is correspondingly further away. There is not enough space around the nitrogen atom to accomodate five nearest-neighbors, although there is sufficient space available around the phosphorus atom[111a].

The population of the d-AOs (cf. Table 4) in H_3NF_2 is 0.05 (D_{3h} symmetry), which is the same as that in other "normal valent" compounds; in contrast, in H_3PF_2 the value is 0.27. This is nevertheless much lower than that required by *Pauling*'s sp^3d hybridization model, namely 1 d-electron. *Rundle*'s model based on an electron-rich multicenter bond is certainly closer to the real situation[111b].

Table 4. Mulliken gross population of the d-AOs in analogous molecules with atoms from the first or second rows [a].

	H_3N	H_3NF_2	H_3NO	H_2NOH		
at N	0.01	0.05	0.08	0.05		
at F, O		0.02	0.05	0.05		
	H_3P	H_3PF_2	H_3PO	H_2POH	H_2PF	H_2FPO
at P	0.08	0.27	0.30	0.15	0.13	0.36
at F [b], O		0.02	0.05	0.01		0.05
	H_2S	H_2SO	HSOH	HClO		
at S, Cl	0.05	0.26	0.11	0.08		
at O		0.05	0.01	0.03		

[a] Cf. [104a, 109]; [b] only axial F atoms.

5.3. Backbonding

The MOs shown in the upper part of Figure 16 are linear combinations of the p-AOs perpendicular to the molecular axis. Since all three π-AOs (in each of the two directions) are fully occupied or, in other words, the MOs (π_b, π_n, and π_a) are fully occupied, no overall bond is formed but rather a repulsion results. If, however, a dπ-AO on the central atom participates (dashed line in Fig. 16) and this makes the π_n MO bonding, an overall bonding interaction arises. Because charge is transferred from the central atom to the outer atoms in the σ-bond, whereas in the π-MO the transfer occurs (with d-AO involvement) in the opposite direction, one speaks of backbonding.

In PH_3F_2, the backbonding is relatively weak and corresponds to a population of the dπ-AO of 0.05. It is, however, much stronger in PF_5, where the dπ-AO population is 0.40[112]. Since the σ-bonds in PF_5 remove so much charge from the P atom, the backbonding is particularly effective. In contrast, the population of dσ is hardly larger than that in PH_3F_2 (0.24 as against 0.22 electrons).

To answer the question how realistic *Pauling*'s model is, one need only consider the population of the dσ. The population of dπ, and thus the presence of backbonding, has no place in *Pauling*'s model. The assumption of sp^3d hybrids in PF_5 is thus not even approximately correct and *Rundle*'s model should be given preference in chemistry courses. In this model three equatorial, two-center, two-electron bonds[113] and an axial, three-center, four-electron bond occur in PF_5, together with appreciable stabilization from π-type backbonding.

5.4. PH_5 and SH_4

Unlike PH_3F_2[108], there is currently no experimental evidence for the existence of the parent compound PH_5, although it has been thoroughly investigated quantum-chemically[114, 115]. The D_{3h} structure represents a minimum in the potential hypersurface with a sufficiently high barrier against decomposition into PH_3 and H_2. It should thus at least be metastable. PH_5 is quite a nonrigid molecule; the barrier to pseudorotation (ca. 2 kcal/mol) is of the same order of magnitude as the zero point energy of the vibration which initiates pseudorotation. The probable consequence is that the five H atoms are dynamically equivalent—as in $CH_5^{\oplus}$[116], although this species has an entirely different equilibrium structure.

It is a singularity of the potential surface for the reaction $PH_5 \rightarrow PH_3 + H_2$ that the transition states for a concerted process and for a zwitterionic intermediate $H_4P^{\oplus} \cdots H^{\ominus}$[115] scarcely differ in terms of their energies and that they are not separated by any significant additional barrier.

There is also no experimental evidence for the existence of SH_4. This molecule, too, is metastable with respect to decomposition into $SH_2 + H_2$, i.e. there is only a local minimum in the potential hypersurface. Its equilibrium structure does not, however, have C_{2v} symmetry in analogy with SF_4, as predicted by early quantum-chemical calculations[117], but is rather a flat square pyramid having C_{4v} symmetry with $r(SH) = 1.40$ Å and $\sphericalangle HSH = 155°$[118–120].

5.5. Localizability of Hypervalent Bonds

At first sight it may appear that one major difference between the models of *Pauling*[55] and *Rundle*[105] is that in the former all of the XR bonds, such as those in SF_6, are localized, two-electron, two-center bonds, whereas in the latter model a description only in terms of multicenter bonds is possible. *Hund*'s localization condition[62] is, in fact, ful-

filled if not only the s and p but also the d valence AOs from the central S atom are involved.

If, however, an ab initio calculation is performed and it is attempted to localize the canonical MOs via a unitary transformation according to *Boys*[65], the new MOs formed are astonishingly well localized in each of the bonds, even though *Hund*'s condition is not fulfilled and the occupancy of the d-AOs is substantially smaller than that corresponding to sp^3d^2 (or to sp^3d) hybridization. This observation is quite similar to that made in Section 3.3 in the discussion of the "normal-valent" hydrides MgH_2, AlH_3, and SiH_4, i.e. we observe a marked "hybridization defect" (in this instance a much too small d population) together with a very small "localization defect". As discussed in Section 3.3, this is due to the strong polarity of the XR bonds, i.e. to a significant transfer of charge from X to R. The MOs of the XR bonds are largely localized on the ligands. *Hund*'s localization condition applies strictly only to true covalent bonds. Contrary to *Pauling*'s supposition, the d valence AOs are not needed at all for a description of hypervalent molecules in terms of localized two-center bonds[104c].

6. Semipolar Bonds versus Hypervalence from Multiple Bonds

6.1. Comparison of H_3NO with H_3PO

If one excludes participation of d-AOs from the N or P in the bonding, the bond has to be formulated as semipolar, i.e. as $H_3X^{\oplus}-O^{\ominus}$, in which one electron has been transferred from X to O.

If d-AOs can participate, backbonding is possible in which charge is transferred from O to X. This should make the bond both stronger and less polar. If one full d-AO on X were occupied, one might be tempted to formulate a double bond. However, even in this hypothetical case, the formulation $H_3X=O$ would not be appropriate[66, 134], for there would then certainly not be one σ- and one π-bond (as in $H_2C=O$) but rather one σ-bond and two mutually perpendicular, half π-bonds. It would then be more justified to refer to a partial triple bond rather than to a double bond.

From the results of the population analysis in Table 4, it is seen that the d-AO population in H_3NO is very small and that in H_3PO it is only 0.30. We are thus far removed from the hypothetical case just discussed of a "quasi-double bond".

That an H_3NO species should exist, whereas an H_3NF_2 species does not, arises because the N atom can accomodate four but not five ligands (that the tautomeric H_2NOH is more stable than H_3NO probably explains why H_3NO has not been observed to date, unlike substituted amine oxides R_3NO or F_3NO).

Comparison of H_3NO with H_3PO indicates that the NO bond in H_3NO (1.38 Å) is typical of an NO single bond, whereas the PO bond in H_3PO (1.47 Å) is distinctly shorter than a genuine PO single bond (e.g. a bridging bond in P_4O_{10}: 1.63 Å) and can therefore be viewed as a double bond. If a calculation is performed without any d-AOs, the PO bond length obtained is 1.60 Å, i.e. a single bond, which serves to underline the significance of the d-AOs (despite their relatively small population). The polarity of the PO bond is not consistent with the presence of a double bond (or, more correctly, a partial triple bond). There is an effective charge of +1.33 on the P and −0.97 on the O, which is in much better accord with the presence of a semipolar bond than with that of a double bond (see Table 5).

Table 5. Effective charges (according to *Mulliken*) in analogous molecules with atoms from the first or second rows [a].

	H_3N	$H_3NF_2(D_{3h})$	H_3NO	H_2NOH		
N	+0.16	+0.75	+0.39	+0.08		
O			−0.76	−0.48		
F		−0.65				
	H_3P	H_3PF_2	H_3PO	H_2POH	H_2PF	H_2FPO
P	+0.34	+1.49	+1.33	+0.58	+0.76	+1.82
O			−0.97	−0.56		−1.01
F		−0.56			+0.60	−0.60
	H_2S	H_2SO	HSOH	HClO		
S, Cl	+0.05	+1.05	+0.28	+0.43		
O		−0.92	−0.44	−0.57		

[a] From calculations with d-AOs [104a, 109].

The Mulliken overlap populations (Table 6) and, in particular, the comparison of H_3NO and H_3PO with their respective isomers H_2NOH and H_2POH indicate that the XO bond in H_3NO is weaker than that for a single bond; in contrast, the XO bond in H_3PO is much stronger than that for a single bond. The use of the *Ahlrichs-Heinzmann* population analysis[60], which is here less dependent on the basis set, shows the same trends[109].

Table 6. Mulliken overlap populations for analogous molecules with atoms from the first or second rows [109].

		H_2NOH	H_3NO	H_2POH	H_3PO	HSOH	H_2SO	HClO
without d-AOs	XO	0.54	−0.01	0.20	0.19	0.17	−0.03	−0.16
	XH	0.74	0.73	0.61	0.63	0.54	0.55	0.62
with d-AOs	XO	0.60	0.35	0.35	0.71	0.31	0.47	0.11
	XH	0.74	0.79	0.64	0.75	0.65	0.63	0.69

Table 7 lists the bond energies of a variety of XO bonds both from quantum-chemical calculations[104a] and from thermochemical data[121–124]. The NO and SO bond energies are only slightly larger than the corresponding σ-in-

Table 7. Bond energies for semipolar XO bonds (in kcal/mol).

A) Computed [104a]

H_3NO:	53	H_3PO:	111	H_2SO:	59
		H_2FPO:	127	HClO:	−1 [a]

B) Empirical [121–124]

F_3NO:	66	F_3PO:	129		
		$(CH_3)_3PO$:	139	$(CH_3)_2SO$:	87
		$(C_2H_5O)_3PO$:	148		
		Cl_3PO:	122		

[a] HClO is not bound with respect to $HCl+O(^3P)$, although it does represent a local minimum on the potential hypersurface.

crements (Table 2), while the strength of the semipolar PO bond lies between that for a double and a triple bond.

Assessment of all these criteria leads to the conclusion that H_3PO has a semipolar PO bond which is stabilized by some backbonding to such an extent that in many respects it behaves like a double bond (or rather a partial triple bond).

6.2. Bond Strengthening by Fluorine- or Alkyl-Substitution

A marked variation in properties is observed even for the same type of bonds with different substituents. When speaking of the stabilization of bonding by substitution, it must be pointed out that the mechanisms for alkyl- and fluorine-substitution are quite different. Stabilization by methyl groups arises partly from stabilization of the positive charge and partly from destabilization of the unprotonated bases as a consequence of the steric hindrance of the substituents[125]. In order to prepare the lone pair for the addition of a proton (or for the formation of a semipolar bond), the RPR angle need only be opened slightly, at least to a much lesser extent than the HPH angle in H_3PO. The PO bond, as such, is not strongly influenced[104a].

The use of fluorine as a substituent, on the other hand, leads to the removal of electronic charge from P (or N or S), to a lowering of the energy of the d-AOs, and to a reinforcement of the backbonding. This strengthens the PO bond and reduces its length. The net result is a substantial measure of backbonding, even in F_3NO where the NO bond is unusually short (1.16 Å)[126].

6.3. Ylides

The analogy between phosphane oxides, such as H_3PO, and ylides, such as methylene phosphorane H_3PCH_2, is also of interest. In H_3PCH_2 the PC bond is essentially semipolar with some backbonding[127]. It is remarkable that there is almost free rotation of the CH_2 group with respect to the PH_3 group[127].

If the CH_2 group is replaced by BH_3, there is no doubly occupied AO available for backbonding and hence only one semipolar bond can be formed. One then obtains a very low bond energy for XB and, rather surprisingly, a larger bond energy for NB (27 kcal/mol) than for the BP bond (17 kcal/mol)[128].

In principle, F_4SCH_2 is also an ylide, even though the authors who first reported this compound preferred a formulation with a double bond[23]. One of the arguments used was the short SC separation and another was the high rotational barrier. No quantum-chemical calculation has yet been performed which can finally settle the issue of the bonding in this particular case. We may confidently expect, however, that the backbonding will be especially pronounced and stronger than in ordinary ylides. Since backbonding is possible only at right angles to the CH_2 plane, there will be both one σ- and one π-bond present. In this respect, F_4SCH_4 as well as other ylides such as H_3PCH_2 correspond more to π-electron systems in organic chemistry with one σ and one double bond than do molecules such as F_4SO or H_3PO, where two perpendicular π-bonds are possible and where partial triple bonds rather than double bonds are realized.

6.4. Several Semipolar XO Bonds at the Same X Atom

Just as the bonding behavior of many electron-rich fluorides can be understood—at least qualitatively—by attaching three-center FXF bonds to normal-valent molecules[129], we may also attach semipolar XO bonds to normal-valent compounds. Molecules such as HClO, H_2SO, or H_3PO are in fact of this type. One can further add an additional semipolar XO bond to arrive at $HClO_2$ or H_2SO_2, or one can start from OH-substituted molecules, such as HOCl, to obtain HOClO, $HOClO_2$, $(HO)_2SO$, $(HO)_2SO_2$, or $(HO)_3PO$. Many very well-known inorganic compounds may be formally built up in this way. Accordingly, an understanding of the semipolar XO bond is valuable not only in "exotic" compounds such as the phosphane oxides but also for the interpretation of the electronic structures of the best known acids H_2SO_4 and H_3PO_4 and their salts. Should sulfuric acid be represented according to the first or second of the following two formulations?

In the light of quantum-chemical studies[130], the first (semipolar) structure appears to be closer to reality. The backbonding which is superimposed on this semipolar structure is difficult to depict in a structural formula.

A further question which we may pose is: Why are HNO_3, $NO_3^{\ominus}$ or $CO_3^{2\ominus}$ monomeric, whereas $PO_3^{\ominus}$ or $SiO_3^{2\ominus}$ are polymeric—or at least oligomeric—and why do the ortho-anions $NO_3^{3\ominus}$ and $CO_3^{4\ominus}$ not exist?

In $NO_3^{\ominus}$ or $CO_3^{2\ominus}$ the π-bonds are fairly strong and lead to a significant amount of resonance stabilization. In monomeric $PO_3^{\ominus}$ or $SiO_3^{2\ominus}$ both the π-bonds and resonance are weaker and structures possessing only σ-bonds have a lower energy, especially since further stabilization can be attained by backbonding (which is hardly feasible for first row elements) and appropriate Madelung terms.

A special feature of the oxo acids of phosphorus is that in H_3PO_3, for example, an H atom is bonded to a P atom and not to an O atom, as in H_2SO_3. In this context it should be pointed out that quantum-chemical calculations indicate that H_3PO and H_2POH have almost the same energy, while HSOH is significantly more stable than H_2SO[104a].

It is also interesting to note that, although electron-rich fluorides often have inequivalent sets of fluorine substituents, the O atoms in electron-rich oxides, such as SO_2 and SO_3, are always equivalent. In SO_2 the SO bonds are so strong that isovalent hybridization takes place and the OSO angle is ca. 120° (as demanded by sp^2 hybridization), whereas H_2S or SF_2 have bond angles close to 90°.

7. Conclusions and Outlook

The chemical bond is a highly complex phenomenon which eludes all attempts at a simple description. The distinction we made here between the bonds of "light" and "heavy" main group elements is thus only an approximation to the real situation. Accordingly, the central thesis that the differences in the two classes of elements derive from the different relative spatial positions of the p valence AOs with respect to the s valence AOs should not be taken too literally. The more one attempts to provide detailed descriptions, the more nebulous the differences tend to become. Furthermore, one is also confronted with a number of contradictions, such as that concerning the hybridizations found in H_2O and H_2S, where the differences are much smaller than might be expected from the different valence angles.

In our discussion we have not investigated the basic physical mechanism involved in chemical bonding, but have assumed that chemical bonding is principally associated with the overlapping of atomic orbitals. A rigorous analysis[57, 64, 131–133] would certainly make everything much more complicated.

With some reservations, however, it may be said that the differences in the chemical behavior of the main group elements of the first and higher rows can be explained. We claim that it is rather the higher row elements which behave normally and those from the first row which are anomolous. On the one hand, first row elements display a pronounced tendency to hybridize and, on the other, to form multiple bonds which are surprisingly strong.

Hybridization is very effective in the first row because the radial factors for these and p valence AOs strongly overlap (which is not the case in the higher rows). That isovalent hybridization—which does not increase the valence—is made use of, even though it costs promotional energy, is due only partly to a direct strengthening of the bonds (because of the improved overlap of the hybrid AOs) but, mainly to the possibility of reducing the repulsion of lone pairs of electrons by hybridization. Both of these effects influence the valence angle.

The weakness of the σ-bonds for first row elements is largely due to the repulsions of lone pairs of electrons. This repulsion is included in the σ-increments. The apparent strength of the π-bonds results from a combination of several effects. One of these is that the lone-pair repulsions enter the σ-increments but do not affect the π increments.

Ab initio calculations provide some insights concerning the nature of the bonds in molecules which appear to violate the octet rule. *Rundle*'s model[105], in which three-center, four-electron or other electron-rich bonds play a decisive role, reflects the true situation more accurately than *Pauling*'s model[29, 55] in which, e.g., sp^3d^n hybrids are assumed. Although d-type AOs are very important as polarization functions to correctly describe hypervalent molecules even qualitatively, their population is in general much smaller than that required by the hybridization model. Moreover, the d-AOs are largely involved in rather complicated multicenter bonds, especially in backbonding. The XO bond must be viewed as semipolar in terms of its charge distribution not only in the phosphane oxides or sulfoxides but also in most oxo acids, such as H_2SO_4 and their anions. Although the d-AOs have a strongly stabilizing effect, there is no justification for a formulation involving double bonds, as was the case in the early days of chemistry before the octet rule was known[134]. There is no "valence extension" which would justify the formulation, e.g., of the S atom in SF_6 or H_2SO_4 with six valence bonds since this simply does not occur.

Theoretical chemistry has several tasks. Among these is to provide a qualitative understanding of the chemical bond, which has been the primary aim in this article. However, it is also capable of making quantitative statements on the structure and properties of individual molecules, which is of especial interest when the molecules in question are not yet known. For small molecules, in particular, it is simpler nowadays to use a quantum-chemical calculation to decide if they are stable—or at least metastable—and what structures they possess. A number of examples of unknown molecules such as H_3PO, H_2SO, PH_5, and P_8 have been discussed here. Ab initio calculations are often very helpful precisely for those compounds of the higher row main group elements where a paucity of experimental work has been carried out and where intuition cannot be relied upon. Without a good ab initio calculation, one would hardly have guessed that silaacetylene Si_2H_2[135] has a nonplanar, doubly bridged equilibrium structure with C_{2v} symmetry (with H_2SiSi and nonlinear *trans*-HSiSiH as metastable isomers).

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Appendix 1

Sources for the dissociation energies used (D_0^0 values were used, especially for diatomic molecules, whenever available; otherwise ΔH_0 values were used, or in a few cases even ΔH_{298} values when ΔH_0 values were not tabulated. Since the errors usually amount to several kcal/mol, no standardization has been attempted:

Diatomic hydrides XH with X from the first or second row: "Recommended" D_0 values from ab initio calculations by *Meyer* and *Rosmus*[141]. In general, these agree well with the data of Huber and Herzberg[87]. Values for the monohydrides XH with X from the third to fifth row are from *Huber* and *Herzberg*[87], and only RbH is from *Gaydon*[142].

The polyhydrides XH_n with X from the first or second row have values from JANAF[121], but BeH_2[143], MgH_2[78],

and AlH_3[78] are from ab initio calculations by *Ahlrichs* et al. Values for polyhydrides where X is an element from the third and fourth rows are from *Barin* and *Knacke*[122].

For the monofluorides XF the values are taken from the data of *Huber* and *Herzberg*[87], but those for OF, PF, and SF are from JANAF[121], and TeF, BiF are from *Barin* and *Knacke*[122].

The values for polyfluorides XF_n are taken from JANAF[121], but those for MgF_2, GeF_4, AsF_3, AsF_5, SeF_4, SeF_6, TeF_2, TeF_4, and TeF_6 are from *Barin* and *Knacke*[122]; the values for SrF_2 and BaF_2 from *Rossini* et al.[123] and for SeF_2 and XeF_6 from [144].

The values for homonuclear diatomic molecules are taken from *Huber* and *Herzberg*[87].

Appendix 2

Sources for the energy increments in Table 2:

CC-σ: From ΔH for C_2H_6 and CH_4[124], assuming that the CH contributions in both molecules are identical, we obtain the value 78.9 kcal/mol. Values of around 80 kcal/mol are obtained from the ΔH values for other alkanes, while from the cohesive energy of diamond 85.5 kcal/mol is indicated. The dissociation energy for $C_2H_6 \rightarrow 2\,CH_3$ is 88 kcal/mol[145]. This is larger than the increment for the CC bond because the same bonding energy for each of the CH bonds in C_2H_6 as that in CH_4 has been assumed, which is ca. 2 kcal/mol greater than in CH_3.

CC-π: From ΔH for C_2H_5 and CH_3[124], assuming that the CH increments in C_2H_4 and CH_3 are identical, we obtain 148.7 kcal/mol for the energy of the double bond. Using the σ-increment from C_2H_6 and CH_4, we obtain a π-increment of 69.8 kcal/mol. From the dissociation energy of the C_2 molecule with a double π-bond, 72 kcal/mol per CC π-bond is obtained. A π-increment of ca. 65 kcal/mol is estimated from the ΔH value for acetylene. The dissociation energy for $C_2H_4 \rightarrow 2\,CH_2$ amounts to 167 kcal/mol[145], which together with the dissociation energy of C_2H_6 would give a π-increment of 79 kcal/mol. Even the rotational barrier in ethane can be regarded as a measure of the strength of the π-bond; this is 65 kcal/mol[146].

NN-σ: From ΔH for N_2H_4 and NH_3[124], assuming equivalent NH bonds, we obtain 38 kcal/mol. The dissociation energy for $N_2H_4 \rightarrow 2\,NH_2$ is 56 kcal/mol and for $N_2(CH_3)_4 \rightarrow 2\,N(CH_3)_2$, 42 kcal/mol[145]; the NC bonds are obviously less affected than the NH bonds by the dissociation.

NN-π: From the dissociation energy of N_2 and a σ-increment of 38 kcal/mol, we obtain a π-increment of 94 kcal/mol.

OO-σ: From ΔH for H_2O_2 and H_2O[124], assuming identical OH bonds, the value 35 kcal/mol is obtained. The dissociation energy for $H_2O_2 \rightarrow 2\,OH$ is 51 kcal/mol, whereas that for $(CH_3)_2O_2 \rightarrow 2\,CH_3O$ is 36 kcal/mol[145].

OO-π: Combination of the σ-increment of 35 kcal/mol with D_0 from O_2 yields a π-increment of 83 kcal/mol.

SiSi-σ: From ΔH for Si_2H_6 and SiH_4[124], we obtain 46 kcal/mol and from $Si_2H_6 \rightarrow 2\,SiH_3$, 45 kcal/mol[145]. From the cohesive energy of solid Si[121], we arrive at 54 kcal/mol.

SiSi-π: If we assume both a σ and a π-bond in the Si_2 molecule, then using a σ-increment of 46 kcal/mol we obtain a π-increment of 28 kcal/mol.

PP-σ: From ΔH for P_2H_4 and PH_3 or PH_2[124], we obtain a value of 48 kcal/mol and from ΔH for black phosphorus[122] 53 kcal/mol.

PP-π: $D_0(P_2)$ and the above PP σ-increment lead to a value of 34 kcal/mol.

SS-σ: The ΔH value for $(CH_3)_2S$ and $(CH_3)_2S_2$[124] afford a value of 64 kcal/mol and those for H_2S and H_2S_2, 58 kcal/mol. The dissociation energy for $H_2S_2 \rightarrow 2\,HS$ is 66 kcal/mol and from ΔH for S_8[145] we arrive at 64 kcal/mol.

SS-π: From D_0 for the S_2 molecule and a σ-increment of 64 kcal/mol, we obtain 37 kcal/mol.

GeGe: σ-Increment from ΔH for Ge_2H_6 and GeH_4[124] and π-increment from D_0 for Ge_2.

AsAs: σ-Increment from ΔH for As_4, assuming no ring strain, and π-increment from D_0 for As_2 and from the σ-increment.

SeSe: σ-Increment from Se_6[122] and the π-increment from this and from Se_2[122].

CN: σ-Increment from $(CH_3)_3N$ and CH_4; π-increment from HCN[124].

CO: σ-Increment from CH_3OH, CH_4, and H_2O[124] or from the dissociation $(CH_3)_2O \rightarrow CH_3O + CH_3$[145].

NO: σ-Increment from an ab initio calculation on H_2NOH[104] and from ΔH for NH_3 and H_2O; π-increment from NOF and NF_3[121].

SiC: σ-Increment from $Si(CH_3)_4$ and CH_4[124] (from solid SiC[122] one would estimate a value of 74 kcal/mol); π-increment from the SiC molecule[121].

PC: σ-Increment from $P(CH_3)_3$[124] and CH_4; π-increment from the PC molecule, assuming the presence of a 1.5-fold π-bond.

SC: σ-Increment from $(CH_3)_2S$[124] and CH_4; π-increment from an ab initio calculation[103] on H_2CS. From the CS molecule—assuming the presence of a double π-bond—we obtain a π-increment of 58 kcal/mol.

SiO: σ-Increment is rather uncertain and is taken from $(CH_3)_3SiOSi(CH_3)_3$ and $(CH_3)_4Si$[124]; with the ΔH values of other molecules, strongly differing values are obtained. The π-increment is from an ab initio calculation on H_2SiO[103]. From the SiO molecule a value of 45 kcal/mol would be obtained, assuming the presence of a double π-bond.

PO: σ-Increment from an ab initio calculation on H_2POH[104]; π-increment from the PO molecule in which a 1.5-fold π-bond has been assumed. From P_4O_6[121] one would obtain a σ-increment of 99 kcal/mol.

SO: σ-Increment from an ab initio calculation on HSOH[104]; π-increment from the SO molecule.

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[1] This concept is used as the counterpart of solid-state chemistry. It is not possible here to account for the solid-state chemistry of the higher row main group elements. Much of what is discussed, however, applies to the chemical bonding in solids.

[2] Double bonds will be called "genuine" when, as in ethylene, both a covalent σ- and π-bond is present, and the π component can be constructed from the p-AOs of the atoms involved. "Non-genuine" double bonds are then those consisting of a semipolar σ-bond upon which is superimposed some "backbonding" involving participation of d-AOs, provided certain properties (bond lengths, force constants, etc.) indicate a bond strength corresponding approximately to that of a double bond (cf. Section 7). The double bonds in the molecules C_2 and O_2 play a special role (cf. e.g. [3], p. 131 ff.).

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[62] The Hund localization condition must be fulfilled, i.e. it must hold for each atom that the number of nearest neighbors is equal to the number of valence electrons involved and to the number of available valence AOs. For details see [3], p. 210.
[63] A unitary transformation of MOs is e.g. the conversion of a set ψ_k into a set φ_k according to $\varphi_k = \sum_i U_{kl}\psi_l$, where (provided all parameters are real) $\sum_l (U_{kl})^2 = 1$; $\sum_l U_{kl} U_{ml} = 0$ for $m \neq l$. An example would be $\varphi_1 = \frac{1}{\sqrt{2}}(\psi_1 + \psi_2)$; $\varphi_2 = \frac{1}{\sqrt{2}}(\psi_1 - \psi_2)$. If, within the framework of the SCF approximation, one starts from a wave function for which the ψ_l MOs are doubly occupied, the total wave function is not changed by conversion of the ψ_1 to φ_1 (other than by a physically irrelevant constant factor). For further details see [3], p. 200 or [64].
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$$\psi_1 = c_1 s + c_2(h_1 + h_2 + h_3)$$

$$\psi_2 = c_3 p_x + \sqrt{2}\, c_4(h_1 - \tfrac{1}{2}h_2 - \tfrac{1}{2}h_3)$$

$$\psi_3 = c_3 p_y + \sqrt{\tfrac{3}{2}}\, c_4(h_2 - h_3)$$

$$d_l = \frac{c_2 - c_4}{c_2 + 2c_4}; \quad d_{hy} = \frac{c_1 - c_3}{c_1 + 2c_3}; \quad \langle hy|hy\rangle = \frac{c_1^2 - c_3^2}{c_1^2 + 2c_3^2}$$

For tetrahedral XH_4 molecules the following relations hold:

$$\psi_1 = c_1 s + c_2(h_1 + h_2 + h_3 + h_4)$$
$$\psi_2 = c_3 p_x + c_4(h_1 + h_2 - h_3 - h_4)$$
$$\psi_3 = c_3 p_y + c_4(h_1 - h_2 - h_3 + h_4)$$
$$\psi_4 = c_3 p_z + c_4(h_1 - h_2 + h_3 - h_4)$$

$$d_l = \frac{c_2 - c_4}{c_2 + 3c_4}; \quad d_{hy} = \frac{c_1 - c_3}{c_1 + 3c_3}; \quad \langle hy|hy\rangle = \frac{c_1^2 - c_3^2}{c_1^2 + 3c_3^2}$$

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A Convenient Method for the Preparation of 1-(*tert*-Butyloxycarbonyl)pyrroles**

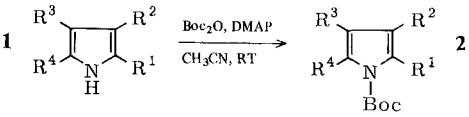
By *Leif Grehn* and *Ulf Ragnarsson**

In connection with structure-activity studies on the antiviral antibiotic distamycin A[1], we prepared analogues without an alkyl substituent on the pyrrole nitrogen and noticed that under certain conditions marked pyrocoll formation occurred[2]. We believed that the *tert*-butyloxycarbonyl (Boc) moiety might serve as a satisfactory protecting group for the pyrrole nitrogen, since deprotection with trifluoroacetic acid (TFA) is compatible with our synthetic scheme[2]. We report here a mild, fast and convenient procedure which gives 1-Boc-pyrroles in excellent yields.

The two Boc derivatives **2a**[3] and **2i**[4] were previously prepared by generating the corresponding anion with a strong base and subsequent treatment with $BocN_3$. Preliminary experiments, however, indicated that treatment of **1h** with $BocN_3$ or Boc_2O in benzene in the presence of KO-*t*Bu/[18]crown-6 resulted in incomplete reaction accompanied with formation of tar. Less severe conditions, successful for protection of tryptophan[5], were also discouraging: Thus, when **1h** was allowed to react with $BocN_3$ in CH_2Cl_2 in the presence of excess solid NaOH and the phase transfer catalyst tetra-*n*-butylammonium hydrogen sulfate, only discolored mixtures of **1h** and **2h** were formed. Even after prolonged reaction time, no trace of **2h** could be detected on treatment of **1h** with $BocF/NEt_3$ in anhydrous ether[6].

An interesting method for the 1-acetylation of pyrrole derivatives has been published[7], and a slight modification (Scheme 1) of this procedure proved successful in converting a wide range of pyrroles into the corresponding 1-Boc-derivatives. When **1h** was allowed to react with Boc_2O in CH_2Cl_2 with NEt_3 as base in the presence of the powerful acylation catalyst 4-dimethylaminopyridine (DMAP)[8–11], pure **2h** was obtained in 89% yield. The reaction also proceeded without base since liberation of CO_2 shifted the equilibrium to the product side. Catalytic amounts of DMAP were, however, required, and Boc_2O could not be replaced by $BocN_3$ in this reaction.

Under these conditions **1b**, **1c** and **1f—1j** reacted smoothly, affording **2b**, **2c** and **2f—2j** in satisfactory yields; however **1a**, **1d** and, particularly, **1e** reacted more slowly and ethyl 5-nitropyrrole-2-carboxylate was completely inert. CH_3CN and CH_2Cl_2 appear to be the solvents of choice and, at least among the more unreactive substrates, CH_3CN was more propitious. Other common solvents seemed less suitable in this reaction.



a, R^1–R^4 = H; **b**, R^1 = CO_2Et, R^2–R^4 = H;
c, R^1 = $COCCl_3$, R^2–R^4 = H; **d**, R^1 = CO_2Et, R^4 = Me, R^2, R^3 = H; **e**, R^1 = CO_2Et, R^2, R^4 = Me, R^3 = H; **f**, R^1, R^3 = CO_2Et, R^2, R^4 = Me; **g**, R^1 = CO_2Bzl, R^3 = NO_2, R^2, R^4 = H;
h, R^1 = CO_2Bzl, R^3 = BocNH, R^2, R^4 = H

1i, Indole; **1j**, 3-Methylindole

Scheme 1.

Table 1. Yields and physical data of the Boc-derivatives **2a—2j** [l].

2 [a]	Yield [%] [c]	M.p. (B.p.) [°C] ([°C/torr]) [f]	^{1}H-NMR ($CDCl_3$, rel. TMS), δ-values
a	81	(79—80/10) [g]	7.23 (t, 2H), 6.21 (t, 2H), 1.59 (s, 9H)
b	85	9.5—10.5 [h] (89—91/0.09)	7.31 (q, 1H), 6.82 (q, 1H), 6.16 (t, 1H), 4.30 (q, 2H), 1.58 (s, 9H), 1.35 (t, 3H)
c	81	8—9 [h]	7.48 (q, 1H), 7.28 (q, 1H), 6.26 (q, 1H), 1.58 (s, 9H)
d	94 [d]	27.5—28 [h]	6.76 (d, 1H), 5.89 (q, 1H), 4.28 (q, 2H), 2.36 (br. s, 3H), 1.59 (s, 9H), 1.33 (t, 3H)
e	94 [d]	5—6 [h]	5.75 (br. s, 1H), 4.30 (q, 2H), 2.31 (d, 3H), 2.19 (s, 3H), 1.56 (s, 9H), 1.34 (t, 3H)
f	81	32—32.5 [h]	4.33 (q, 2H), 4.30 (q, 2H), 2.60 (s, 3H), 2.45 (s, 3H), 1.59 (s, 9H), 1.36 (t, 6H)
g [b]	87	100.5—101.0 [i]	8.06 (d, 1H), 7.38 (s, 5H), 7.29 (d, 1H), 5.31 (s, 2H), 1.57 (s, 9H)
h	80 [e]	126—126.5 [i]	7.36 (pert. signal, 6H), 6.70 (d, 1H), 6.31 (br. s, 1H), 5.26 (s, 2H), 1.52 (s, 9H), 1.49 (s, 9H)
i	82	(113—114/0.2) [j]	8.15 (m, 1H), 7.56 (m, 2H), 7.26 (m, 2H), 6.56 (q, 1H), 1.66 (s, 9H) [k]
j	93	(131—132/0.75) [l]	8.11 (m, 1H), 7.56—7.20 (m, 4H), 2.26 (d, 3H), 1.65 (s, 9H)

[a] All new compounds gave satisfactory elemental analyses (C,H,N). [b] For synthesis of starting material, see [14]. [c] Crude product. [d] DEAEA-treatment omitted. The crude product contained a few % Boc_2O (^{1}H-NMR). [e] CH_2Cl_2 as solvent gave 89% yield. [f] Uncorrected. [g] Lit. [3]: 91—92°C/20 torr. [h] From petroleum ether. [i] From CH_2Cl_2/petroleum ether. [j] Lit. [4]: 110°C/0.08 torr. [k] Not consistent with published spectrum [4]. [l] Experimental: DMAP (122 mg, 1.00 mmol) and Boc_2O (2.62 g, 12 mmol) were added to a stirred solution (or suspension) of **1a—1j** (10 mmol) in dry CH_3CN (10—20 mL) at RT. Evolution of gas commenced, and after a few minutes a clear solution was obtained. After 1 h, all starting material had been consumed (TLC); **1a** and, particularly, **1e** required at least 15 h for complete reaction. For **2a—2c**, **2f**, **2i**, and **2j**, excess Boc_2O was destroyed by DEAEA (349 mg, 3.0 mmol) (10 min stirring). The crude products were obtained by partitioning between ether (100 mL) and 1 M $KHSO_4$ (50 mL), washing the ether extract with 25 mL portions of 1 M $KHSO_4$ (5×), water (1×), 1 M $NaHCO_3$, and brine (3×), and subsequent drying ($MgSO_4$). The solids **2g**, **2h** were washed with cold petroleum ether (40/60) to remove excess Boc_2O and then crystallized. The oily **2a—2f**, **2i**, and **2j** were dissolved in petroleum ether, treated with Norite, and evaporated to dryness (**2a** volatile!), affording colorless oils. Products **2a**, **2b**, **2i**, and **2j** were distilled under reduced pressure. Analytically pure samples of **2b—2f** were obtained by crystallization from petroleum ether (10 mL/g, −70°C).

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The work-up procedure (Table 1) was sometimes simplified by trapping excess Boc_2O in the reaction mixture by brief treatment with 2-diethylaminoethylamine (DEAEA) followed by acid extraction[12]. Excess DEAEA and extended reaction times should, however, be avoided in these work-ups, since many Boc-pyrroles are decomposed by strong bases. Thus, **2g** decomposed completely within 5 min in CH_3CN at room temperature in the presence of a slight excess of DEAEA.

The TFA-mediated removal of Boc from **2h** proceeded smoothly, affording essentially pure benzyl 4-aminopyrrole-2-carboxylate. By means of our previously described procedure[13], **2f** was reconverted into **1f** in 97% yield. When **2j** was treated with TFA (RT, 2 min), 3-methylindole-1-carboxylic acid could be isolated in 90% yield. Decarboxylation was effected by refluxing in benzene, giving pure **1j** as the sole product.

In view of these findings, the possibility of utilizing the Boc-group for protecting the indole moiety in tryptophan has been considered. Although recent work has suggested the 2,2,2-trichloroethoxycarbonyl (Troc) and the benzyloxycarbonyl (*Z*) groups as suitable tryptophan-protecting groups[5], the Boc-group could be advantageous in some cases.

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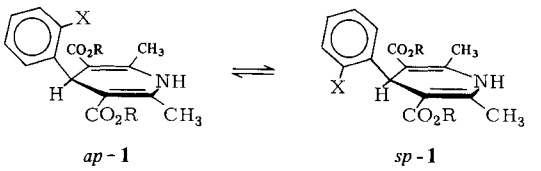
[14] The starting material was prepared from 4-nitro-2-pyrrolecarboxylic acid by analogy to the synthesis of **1h** [2]. The yield of crude product containing a nonpolar impurity was 84%. Recrystallization from toluene (50 mL/g, Norite) afforded pure **1g** as white crystals: m.p. = 149.5–150.5°C; ^{1}H-NMR ($CDCl_3$): $\delta = 7.73$ (q, 1H), 7.40 (pert. s, 6H), 5.35 (s, 2H).

Rotational Barriers of 4-Aryl-1,4-dihydropyridines (Ca Antagonists)

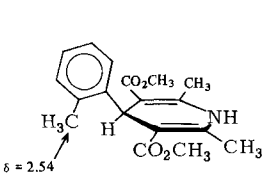
By *Siegfried Goldmann** and *Walter Geiger*

In recent years, 1,4-dihydropyridines **1** have gained considerable importance as calcium antagonists (e.g. nifedipine ($R = CH_3$, $X = NO_2$), the biologically active constituent of Adalat®)[1]. These compounds occur either as the *sp*-rotamer, in which the substituent X and the hydrogen atom at the 4-position are *synperiplanar*, or as the *ap*-rotamer, in which X and the aforementioned hydrogen atom are *antiperiplanar*.

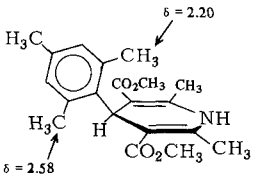


ap-**1** ⇌ *sp*-**1**

Whereas rotamers can be detected in the analogously structured 9-arylfluorenes[2], they have not been observed in the 1,4-dihydropyridines **1**[3]. To gain information about the "pharmacologically active conformer", we synthesized the model compounds **1a**[4] and **2**[5] and showed that the *ap*- and *sp*-forms exist in a rapidly established equilibrium which, however, lies heavily in favor of the *sp*-form.



1a



2

The 200 MHz ^{1}H-NMR spectrum of **2** at room temperature displays a broad singlet at $\delta = 2.39$ ($CDCl_3$) for the two *ortho*-methyl groups. Upon cooling the solution, coalescence occurs at $-18°C$ ($\Delta G^+(-18°C) = 51.1$ kJ/mol), whereas two separate signals ($\delta = 2.20$, 2.58) are observed at $-50°C$. Compared to the analogous fluorene ($\Delta G^+ > 96$ kJ/mol)[2], the dihydropyridine **2**, therefore, has a considerably lower rotational barrier.

Information about the position of the equilibrium *sp*-**1a** ⇌ *ap*-**1a** is provided by the 200 MHz ^{1}H-NMR spectra of **2**[5] and **1a**[4]. The chemical shift of the signal of the methyl group in the 2′-position of **1a** ($\delta = 2.54$) is independent of temperature and agrees well with that of the deshielded methyl group in the low-temperature spectrum of **2** ($\delta = 2.58$). Consequently, **1a** is predominantly present in solution in the synperiplanar conformation[6].

In 1,4-dihydropyridines of structure **1** the *ap*- and *sp*-forms therefore exist in a rapidly established equilibrium resulting from a low rotational barrier; the *sp*-form of the thermodynamically more stable rotamer[7] is even more favored than in 9-arylfluorenes[2].

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CAS Registry numbers:
1a, 73257-44-0; **2**, 89378-44-9; 2,4,6-trimethylbenzaldehyde, 487-68-3; methyl acetoacetate, 105-45-3.

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[4] J. Aritomi, S. Ueda, H. Nishimura, *Chem. Pharm. Bull. 28* (1980) 3163. ^{1}H-NMR ($CDCl_3$, TMS): $\delta = 2.32$ (6H), 2.54 (3H, 2′-CH_3), 3.61 (6H), 5.14 (1H), 5.57 (NH), 7.0 (3H), 7.30 (1H).
[5] **2**: A mixture of 2,4,6-trimethylbenzaldehyde (74.1 g, 0.5 mol), methyl acetoacetate (11.6 g, 0.1 mol), and conc. aqueous ammonia (5 mL) in 300 mL ethanol is refluxed for 15 h, the ethanol subsequently removed, and excess 2,4,6-trimethylbenzaldehyde distilled over a column. The thus purified 2,4,6-trimethylbenzaldehyde (44.7 g, 0.3 mol), methyl acetoacetate (69.6 g, 0.6 mol) and conc. aqueous ammonia (33 mL) are then refluxed in 200 mL ethanol for 20 h, all volatiles removed using an oil vacuum pump,

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and the intensely fluorescent product isolated on silica gel with chloroform. Yield 0.1 g (0.1%), m.p. = 180–182°C. ^{1}H-NMR ($CDCl_3$, TMS, 20°C): δ = 2.17 (6H), 2.18 (3H), 2.39 (br, 2',6'-CH_3), 3.51 (6H), 5.43 (NH), 5.52 (1H), 6.73 (2H).

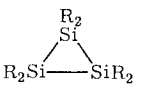
[6] The synperiplanar conformation could be confirmed via a nuclear Overhauser effect at the C-4 hydrogen atom (Dr. *J. Kurz* is thanked for this measurement).

[7] The *sp*-form is also adopted preferentially in the crystal lattice, cf. also: F. Bossert, 2nd Int. Adalat Symp., Springer, Berlin 1975, p. 24; R. Fossheim, K. Svarteng, A. Mostad, C. Romming, E. Shefter, D. J. Triggle, *J. Med. Chem. 25* (1982) 126; A. M. Triggle, E. Shefter, D. J. Triggle, ibid. *23* (1980) 1442.

Hexa-*tert*-butylcyclotrisilane, a Strained Molecule with Unusually Long Si–Si and Si–C Bonds**

By *Annemarie Schäfer, Manfred Weidenbruch*, Karl Peters,* and *Hans-Georg von Schnering**

The compounds **1a**[1] and **1b**[2], the first examples of the long sought cyclotrisilanes $(R_2Si)_3$, were recently obtained in low yield; **1a** was also characterized by X-ray structure analysis[1].



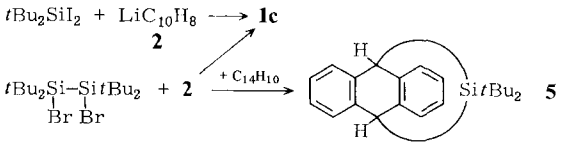
1a, R = 2,6-Dimethylphenyl
1b, R = Neopentyl
1c, R = *tert*-Butyl

Here, we report the synthesis, properties, and structure of hexa-*tert*-butylcyclotrisilane **1c**, which is astonishingly readily accessible and which differs markedly in both its properties and structure from those of **1a** and **1b**. Compound **1c**, which is air-stable and does not decompose even when heated to its melting point of 180°C, is formed by dehalogenation of di-*tert*-butyldiiodosilane with lithium dihydronaphthylide **2** and can be isolated as colorless, prismatic crystals by column chromatography[3].

The high symmetry of **1c** in solution is reflected in the temperature-dependence of the ^{1}H-NMR spectrum, in which, in contrast to those of **1a** and **1b**, the singlet from the methyl protons is not split at −70°C. Irradiation of **1c** in methanol yields equimolar amounts of di-*tert*-butylmethoxysilane **3** and 1,1,2,2-tetra-*tert*-butyl-1-methoxydisilane **4**, which suggests formation of di-*tert*-butylsilanediyl and tetra-*tert*-butyldisilene[4] as initial products of the photolysis.

$$\mathbf{1c} + 2\,CH_3OH \xrightarrow{h\nu} t\mathrm{Bu_2SiH(OCH_3)} + t\mathrm{Bu_2(CH_3O)Si{-}SiH}t\mathrm{Bu_2}$$

Additional evidence for the formation of the silanediyl as an intermediate is provided by the photochemical reaction of **1c** with triethylsilane, from which the insertion product 1,1-di-*tert*-butyl-2,2,2-triethyldisilane can be isolated. The reaction of 1,2-dibromo-1,1,2,2-tetra-*tert*-butyldisilane with **2** also gives access to **1c**; the silanediyl intermediate can be trapped as the product of addition **5** with anthracene[5].



X-ray structure analysis of **1c** revealed unexpected details (Fig. 1). The molecule possesses complete 32 symmetry (D_3) with Si–Si distances of 251.1(3) pm in the three-membered ring—the largest Si–Si distance yet found in a molecule—and also exhibits very large Si–C distances of 197.0(5) pm to the *tert*-butyl groups. These distances exceed those observed in **1a** by 10 and 6 pm, respectively, and, compared to the normal single bond lengths (Si–Si 235 pm, Si–C 188 pm), correspond to Pauling's bond order (PBO) of 0.60 and 0.75, respectively. The Si–Si distance would therefore be equivalent to a C–C distance of 170 pm! In contrast, the peripheral C–C bonds of 153.8 pm are normal and exhibit no counteraction for the loss of bond strength in the central three-membered ring. Accordingly, the molecule is unusually highly strained and energy rich. The strain is also displayed in the bond angles (Fig. 1), e.g. Si–C–C_i (112.1°) > C_i–C–C_j (106.7°), or C–Si–C (105.7°).

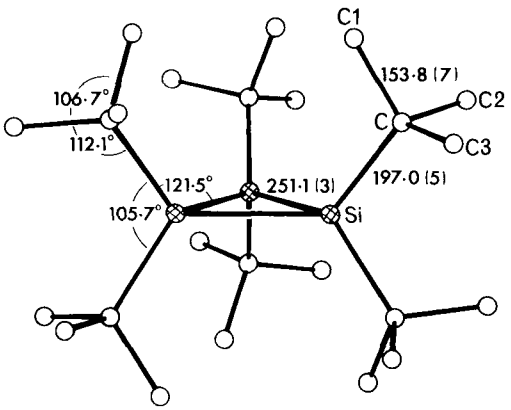


Fig. 1. Structure of the cyclotrisilane **1c** showing bond lengths [pm] and bond angles. The compound crystallizes rhombohedrally, space group $R\bar{3}c$ (No. 167) with a_r = 1745.7(5) pm, α = 33.03(3)° or a_n = 992.4(2), c = 4947.0(10) pm, and Z = 2 or 6 ($Mo_{K\alpha}$ radiation, four-circle diffractometer 722 hkl with $F > 3\sigma(F)$; R = 0.067; no atoms exhibit anomalous deviations from isotropic behavior; H atoms positioned isotropically.

The ease of formation of **1c** can almost certainly be ascribed to the crystallization of LiI, but also to the trisilacyclopropane system which is sterically favorable for directly adjacent bulky substituents. Once formed, the molecule is eminently shielded by its substituents. The substituents sheath the central Si_3 system with optimal special requirements, and thus generate the chirality and rigidity via mutual steric accomodation (Fig. 1). Both enantiomers occur in the crystal. The molecules adopt a cubic close packing of spheres arrangement of periodicity 2 with alternating layers of the two enantiomers.

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[3] Procedure: A solution of **2** (50 mmol) in 70 mL THF (tetrahydrofuran) is added dropwise to a solution of di-*tert*-butyldiiodosilane (8.5 g, 21.5 mmol) in 70 mL THF at −78 °C and the mixture warmed up to room temperature. After removal of THF by distillation, the residue is taken up in 40/60 petroleum ether, LiI filtered off, and naphthalene sublimed out in vacuo. Column chromatography of the crude product on silica gel 60 using 40/60 petroleum ether affords 2.2 g (72%) **1c**, m.p. = 182 °C (decomp.), as colorless prisms. ^{1}H-NMR (80 MHz, C_6D_6): $\delta = 1.40$ (s). ^{13}C-NMR (C_6D_6): $\delta = 31.04$ (C_q), 34.57 (C_p). MS (EI): *m/z* 426 (20%, M^+). UV: $\lambda_{max} = 215$, 240, 340, 390 nm.

[4] **3**: B.p. = 60—65 °C/50 mbar. ^{1}H-NMR (80 MHz, $CDCl_3$): $\delta = 1.06$ (s, 18 H), 3.65 (s, 3 H), 3.98 (s, 1 H). **4**: cf. S. Masamune, S. Murakami, H. Tobita, *Organometallics 2* (1983) 1464.

[5] **5**: M.p. = 195—201 °C. ^{1}H-NMR (80 MHz, $CDCl_3$): $\delta = 0.65$ (s, 18 H), 3.80 (s, 2 H), 7.1 (m, 8 H). MS (EI): *m/z* 320 (11%, M^+), 263 (21, $M^+ - 57$), 207 (22, $M^+ - 113$), 178 (100, $C_{14}H_{10}^+$), 142 (45, tBu_2Si^+).

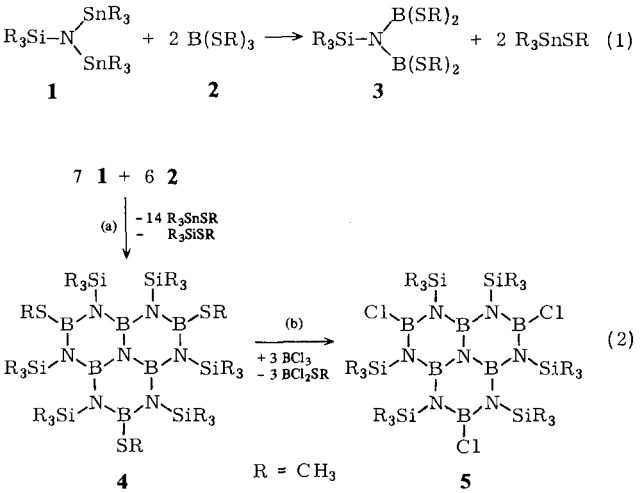
[6] Further details of the crystal structure analysis can be obtained from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen, Germany, by quoting the depository number CSD 50626, the names of the authors and the journal citation.

Synthesis and Structure of a B_6N_7 Phenalene**

Von *Theo Gasparis-Ebeling* and *Heinrich Nöth**

Annelated polycyclic arenes are steps on the route from benzene to graphite. In contrast, in the isoelectronic series of BN heterocycles only B_3N_3-benzene (borazine)[1], B_5N_5-naphthalene[2] are known in addition to boron nitride $(BN)_\infty$[3]. We have now found a surprisingly facile route to a further annelated BN system, a B_6N_7 phenalene.

In the reaction of the distannylamine **1** with tris(methylthio)borane **2**, we expected to isolate the diborylamine **3**. However, the reaction, which commences at 50 °C and which was carried out at 110 °C in the presence of a large excess of **2**, yields the derivative **4** of a B_6N_7 phenalene[4] as shown in (2a). Treatment of **4** with BCl_3 as described by (2b) leads to selective cleavage of the methylthio moieties to give the derivative **5**.



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[**] Contributions to the Chemistry of Boron, Part 144. - Part 143: C. K. Narula, H. Nöth, *Inorg. Chem.*, in press.

The 70 eV mass spectrum of compound **4** exhibits an intense molecular ion with correct isotopic pattern. Although **4** and **5** each contain two sets of magnetically nonequivalent B atoms, in the ^{11}B-NMR spectra (64.3 MHz) at room temperature only one signal is observed in each case (**4**: $\delta^{11}B = 39.4$, $w_{1/2} = 530$ Hz, asymm.; **5**: $\delta^{11}B = 31.5$, $w_{1/2} = 320$ Hz)[5]. The structure proposed for **4** and **5** are, however, unequivocally confirmed by the ^{1}H- and ^{13}C-NMR spectra (**4**: $\delta^1H = 0.29$, 2.26 (3 : 1), $\delta^{13}C = 4.61$, 13.31; **5**: $\delta^1H = 0.39$, $\delta^{13}C = 4.61$).

According to X-ray structure analysis[6], **4** possesses the point group symmetry C_3: the threefold rotational axis of the molecule coincides with the threefold crystallographic axis. Although all the ring atoms can be considered to be sp^2-hybridized, the B_6N_7 framework is nonplanar (cf. Fig. 1). This principally arises from the presence of the bulky trimethylsilyl groups, whose effective radii would overlap considerably in a planar structure: the normals to the B_2NSi planes enclose an angle of 94.7°. The central BN distance corresponds to that found in borazines[7]. With the exception of B2—N1′, all the remaining BN distances, in particular the BN(Si) distances to the B1 atom, are longer than the central BN distance. Associated with this is an increase in the exocyclic N2-B1-N1 angle and of the endocyclic dihedral angles (N1-B1-N-B1′ 18.5°, N2-B1-N-B1′ 15.8°, N-B1-N1-Si1 122.8°, N2-B1-N1-Si1 −59.1°, N-B1-N2-Si2 126.9°, N1-B1-N2-Si2 −51.2°, N1-B1-N2-B2 148.6°, N1′-B2-N2-B1 17.9°, S-B2-N2-Si2 39.2°, S-B2-N1′-Si1′ 39.0°). The BN π-interaction should, in consequence, be weaker in this region of the 14π-electron system relative to that in the central BN bonds. Thus, the structure corresponds to a sterically strongly strained periphery, bonded to a "normal" central moiety.

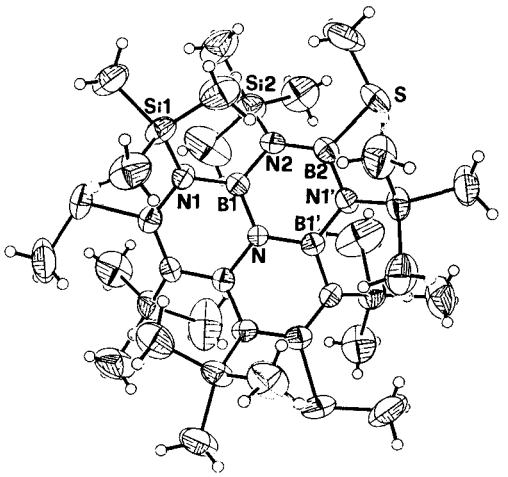

Fig. 1. ORTEP representation of the molecular structure of **4** in the crystal. Selected bond lengths [Å] and angles [°]: N-B1 1.443(2), B1-N1 1.450(4), B1-N2 1.471(5), B2-N1′ 1.434(4), N2-B2 1.448(5), B2-S 1.855(5), N1-Si1 1.788(3), N2-Si2 1.767(3); B1-N-B1′ 120.0(1), N-B1-N1 116.7(3), N-B1-N2 117.5(2), N1-B1-N2 125.7(2), N2-B2-S 123.4(2), N2-B2-N1′ 122.6(3), N1′-B2-S 113.9(3–, B1-N1-Si1 121.0(2), B1-N1-B2′ 115.7(2), Si1-N-B2′ 119.0(2), B1-N2-B2 113.7(2), B1-N2-Si2 116.5(2), B2-N2-Si2 126.2(2).

5 is a propitious educt for the synthesis of the parent compound $B_6N_7H_9$ with the phenalene framework; this compound could be used, inter alia, to test whether, in contrast to **4**, the unsubstituted molecule is planar.

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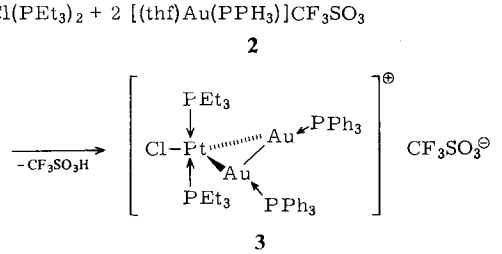
[1] *Gmelin Handbuch der Anorganischen Chemie, 8th edit., 1st Suppl., vol. 2,* Springer-Verlag, Berlin 1980, p. 110ff.; *ibid. vol. 51,* 1978, p. 25ff.
[2] A. W. Laubengayer, P. C. Moews, R. F. Porter, *J. Am. Chem. Soc. 83* (1961) 1337; L. J. Turbini, R. F. Porter, *Inorg. Chem. 14* (1975) 1252.
[3] Cf. [1a], p. 1ff.
[4] *2,3,5,6,8,9-Hexahydro-2,5,8-tris(methylthio)-1,3,4,6,7,9-hexakis(trimethylsilyl)-1H,4H,7H-1,3,4,6,7,9,9b-heptaaza-2,3a,5,6a,8,9a-hexaboraphenalene* **4**: $B(SMe)_3$ **2** (11.41 g, 75 mmol) is added dropwise to a solution of $Me_3SiN(SnMe_3)_2$ **1** (27.8 g, 20 mmol) in 50 mL toluene at −20°C. The mixture is then stirred for 2 d at room temperature and refluxed for a week. At the end of this time all volatiles are removed under reduced pressure (30°C/1 torr). Recrystallization of the residue from pentane affords 6.15 g (86%) **4**, m.p. = 345°C. **4** was characterized by elemental analysis, and by mass and NMR spectroscopy; **5** only by NMR spectroscopy, m.p. > 300°C.
[5] For BN_3 groups in borazines, $\delta^{11}B = 29$, for SBN_2 groups $\delta = 36$—37, and for $ClBN_2$, $\delta \approx 31$.
[6] $C_{21}H_{63}B_6N_7Si_6S_3$, $M_r = 743.4$: $a = b = 20.236(5)$, $c = 18.839(5)$ Å, $V = 6680.9$ Å^3, $Z = 6$, hexagonal setting, space group R3c. $Mo_{K\alpha}$ irradiation, graphite monochromator, empirical absorption correction, scan width 0.7°, variable scan speed (2.3—29.3°/min); 5767 measured reflections over the range $2.5 < 2\vartheta < 50°$, 2408 unique reflections, structure solved using direct methods. Anisotropic refinement of all atoms other than hydrogen, H-atoms isotropic with calculated atomic positions (17H atomic positions localized from difference Fourier synthesis), $R = 0.0422$ for 174 free variables, $R_w = 0.0415$. Further details on the crystal structure analysis can be obtained from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2 by quoting the depository number CSD 50692, the names of the authors, and the journal citation.
[7] Borazine: BN 1.435 Å; W. Harsberger, G. Lee, R. F. Porter, S. H. Bauer, *Inorg. Chem. 8* (1969) 1683; *B,B',B''*-tris(dimethylamino)borazine: BN_{endo} 1.433, BN_{exo} 1.429 Å; H. Hess, B. Reiser, *Z. Anorg. Chem. 381* (1971) 91.

Synthesis of the First Pt-Au Cluster by an Unexpected $H^{\oplus}$-Substitution at *trans*-PtH(Cl)L_2**

By *Pierre Braunstein*, Hans Lehner, Dominique Matt, Antonio Tiripicchio,* and *Marisa Tiripicchio-Camellini*

Monohydrido complexes *trans*-PtH(Cl)L_2 (L = phosphane) are known to undergo easy substitutions either of the chloride with anionic species (carbanions[1], carbonylmetallates[2]), leading to complexes in which the hydride ligand remains attached to the platinum, or of the hydride (e.g. with chloride ions (with HCl))[3]. We report here an unusual example of a substitution in which the hydride ligand is replaced by an Au_2 fragment.



When *trans*-PtHCl$(PEt_3)_2$ **1** is allowed to react with two equiv. $[(thf)Au(PPh_3)]CF_3SO_3$ **2**, (thf) = tetrahydrofuran, the $PtAu_2$ cluster **3** is formed in nearly quantitative yield[9].

The $^{31}P\{^1H\}$-NMR spectrum of **3** shows two sets of resonances centered at $\delta = 42.0$ and 35.7, which correspond to the two PPh_3 and the two PEt_3 ligands, respectively. Both sets of resonances appear as a central triplet ($^3J_{P,P} \approx 4$ Hz) with corresponding platinum satellites ($^1J_{P,Pt} = 2197$ Hz and $^2J_{P,Pt} = 792$ Hz).

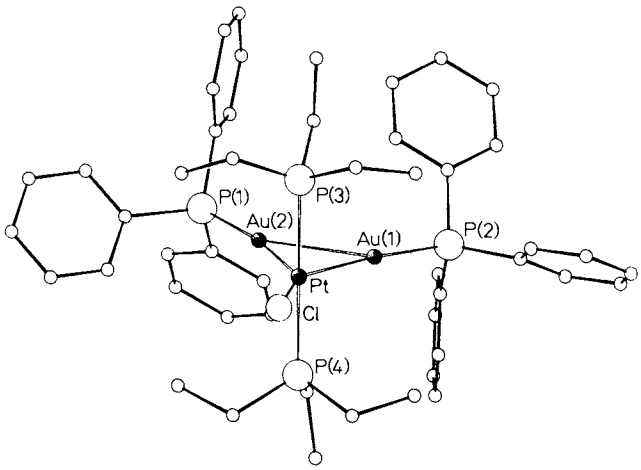


Fig. 1. Structure of **3** in the crystal [4]. Selected distances [Å] and angles [°]: Au1—Au2: 2.737(3), Pt—Au1: 2.600(3), Pt—Au2: 2.601(4), Au1—P2: 2.261(10), Au2—P1: 2.264(7), Pt—Cl: 2.396(11), Pt—P3: 2.298(9), Pt—P4: 2.298(9), Pt—Au1—Au2: 58.2(1), Pt—Au2—Au1: 58.2(1), Au1—Pt—Au2: 63.5(1), Pt—Au1—P2: 173.1(3), Au2—Au1—P2: 128.6(3), Au1—Au2—P1: 136.6(3), Pt—Au2—P1: 165.1(3), P3—Pt—P4: 178.3(4), Au1—Pt—Cl: 148.6(3), Au2—Pt—Cl: 147.9(3).

The X-ray structure determination (Fig. 1)[4] reveals an isosceles triangle for the metal core with a pentacoordinated Pt atom and two tricoordinated Au atoms. The Pt—Au separations (ca. 2.601 Å) are consistent with metal-metal bonds. Although complexes containing Au-transition metal bonds have previously been characterized[5], **3** is, to our knowledge, the first fully characterized compound with a Pt—Au bond. The distance between the two Au atoms (2.737(3) Å) is shorter than in gold metal (2.884 Å) and is one of the shortest reported for Au clusters[6], supporting an Au—Au interaction.

The geometry about the Pt atom is distorted trigonal bipyramidal (P1, P2, Cl, Au1, Au2 and Pt lie almost in the same plane) and is reminiscent of that found recently in bimetallic Pt complexes[7,8]. Together with the short Au—Au distance and the value of the Pt—Au—P angles, this geometry is consistent with the two-electron, three-center (2e3c) bonding shown in Figure 2. **3** is thus similar to the alkyne-metal complexes **4** emphasizing that alkynes RC≡CR and the Au_2 fragment L→Au—Au←L have the same dominant bonding interaction with the Pt center.

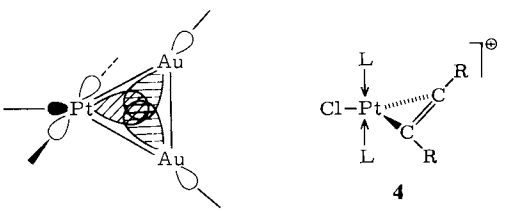


Fig. 2. 2e3c Bond of the metal framework of **3** (left) and structure of the cationic alkyne complex **4**.

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The unexpected reactivity of **1** presumably results from an electron transfer from the Pt atom to $[AuPPh_3]^{\oplus}$ with subsequent elimination of $H^{\oplus}$. The resulting bimetallic PtAu intermediate could then add a further $[AuPPh_3]^{\oplus}$ unit to give **3**. Alternatively, a μ_2-H intermediate might also be involved. This would be relevant to reactivity studies on bimetallic platinum hydride complexes[7].

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CAS Registry numbers:
1, 16842-17-4; **2**, 89346-95-2; **3**, 89346-97-4; $AuCl(PPh_3)$, 14243-64-2; Pt, 7440-06-4; Au, 7440-57-5.

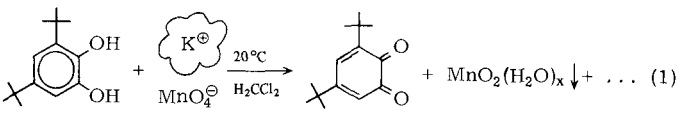
[1] L. Abis, R. Santis, J. Halpern, *J. Organomet. Chem. 215* (1981) 263.
[2] O. Bars, P. Braunstein, *Angew. Chem. 94* (1982) 319; *Angew. Chem. Int. Ed. Engl. 21* (1982) 308.
[3] R. Ros, R. A. Michelin, R. Bataillard, R. Roulet, *J. Organomet. Chem. 161* (1978) 75.
[4] Triclinic space group $P\bar{1}$, $Z=2$, $a=14.209(14)$, $b=21.938(14)$, $c=10.614(5)$ Å, $\alpha=81.65(6)$, $\beta=106.89(7)$, $\gamma=76.57(7)°$, $V=2998(4)$ Å^3, 4204 observed reflections ($I>3\sigma(I)$), $Mo_{K\alpha}$ irradiation, $R=0.062$, $R_w=0.068$. Further details on the crystal structure investigation can be obtained from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2 by quoting the depository number CSD 50764, the names of the authors, and the journal citation.
[5] P. Braunstein, J. Dehand, *J. Organomet. Chem. 88* (1975) C24; P. Braunstein, U. Schubert, M. Burgard, *Inorg. Chem.*, in press, and literature cited therein.
[6] P. G. Jones, *Gold Bull. 14* (1981) 102; C. E. Briant, K. P. Hall, D. M. P. Mingos, *J. Chem. Soc. Chem. Commun. 1983*, 843; E. Roland, K. Fischer, H. Vahrenkamp, *Angew. Chem. 95* (1983) 524; *Angew. Chem. Int. Ed. Engl. 22* (1983) 326.
[7] See e.g.: G. Bracher, D. M. Grove, P. S. Pregosin, L. M. Venanzi, *Angew. Chem. 91* (1979) 169; *Angew. Chem. Int. Ed. Engl. 18* (1979) 155; R. S. Paonessa, W. C. Trogler, *Inorg. Chem. 22* (1983) 1038.
[8] R. Bender, P. Braunstein, A. Tiripicchio, M. Tiripicchio-Camellini, *J. Chem. Soc. Chem. Commun. 1984*, 42.
[9] Experimental: All reactions and operations, including the distillation of the solvents, were carried out under N_2. $AgCF_3SO_3$ (0.260 g, 1.01 mmol) was allowed to react with $AuCl(PPh_3)$ (0.500 g, 1.01 mmol) in 20 mL THF. AgCl was filtered off and the solution was added to **1** (0.235 g, 0.50 mmol) in 10 mL THF. The reaction mixture became yellow and acidic (pH monitoring) and after stirring for 1 min was filtered and concentrated. Addition of hexane and cooling to −15 °C produced **3** as white crystals. Suitable crystals for X-ray diffraction were obtained from CH_2Cl_2/pentane at −15 °C. Yield: 0.709 g (92%); m.p. 148 °C (decomp.). Correct elemental analysis (C, H).

Oxidation Reactions with "Naked" Permanganate Ions under Aprotic Conditions**

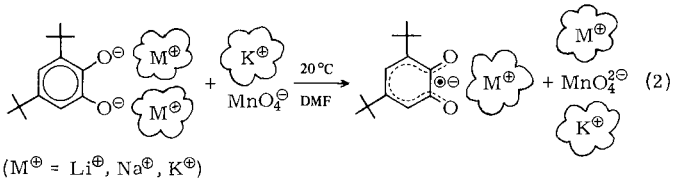
By *Hans Bock** and *Dieter Jaculi*

Dedicated to Professor Heinz Gerischer on the occasion of his 65th birthday

In teaching basic chemistry, water-enveloped $MnO_4^{\ominus}$ anions are introduced as the prototype of pH-dependent oxidation reagents[1a] and are used, inter alia, in "manganometric" analyses. "Naked", i.e. considerably less solvated $MnO_4^{\ominus}$ anions, which occur in aprotic solutions such as "purple benzene", can readily be prepared by lipophilic complexation of the counterions with crown ethers or cryptands and be used for the selective oxidation of organic compounds[1b]; for example, for the synthesis of 3,5-di-*tert*-butyl-*o*-benzoquinone in almost quantitative yield [eq. (1)][1c].



We have reinvestigated[3] this model reaction of catechols, a class of compounds which is also of biochemical interest[2]. Formation of water as a reaction product can be prevented using the dialkali-metal catecholates, obtained either from the catechol by treatment with butyllithium or from the quinone by treatment with sodium- or potassium-amalgam. Under aprotic conditions and with repurified argon as inert gas, reaction (1) proceeds stoichiometrically as a one-electron transfer (2) to yield the semiquinone radical anion, which can be detected in the reaction solution by ESR spectroscopy.



($M^{\oplus}$ = $Li^{\oplus}$, $Na^{\oplus}$, $K^{\oplus}$)

Manganese dioxide is not precipitated since the $MnO_4^{2\ominus}$ dianion does not disproportionate under aprotic conditions[1a]. Subsequent reaction of the semiquinone radical anion with excess $MnO_4^{\ominus}$ is not observed.

Numerous measurements corroborate this unexpected result:

- The half-wave potentials of the dialkali-metal catecholates determined by cyclic voltammetry both in the presence and absence of cryptands (Table 1) and especially the ENDOR spectra of the ion pairs which contain the semiquinone radical anion (Fig. 1) illustrate the influence of the alkali-metal cations[2].

Table 1. Half-wave potentials $E_{1/2}$ [V] and ΔE values [mV] for dialkali-metal 3,5-di-*tert*-butylcatecholates in the absence and presence of cryptands in DMF/$R_4N^{\oplus}ClO_4^{\ominus}$, determined at room temperature relative to SCE (scan rate 100 mV/sec).

$A^{2\ominus}$ [a] 2 $M^{\oplus}$ [Cryptand]	$E^{(1)}_{1/2}$	ΔE	$E^{(2)}_{1/2}$	ΔE
$Li^{\oplus}$	−0.29	100	−0.74	100
+[2.1.1]	−0.44	80	−1.1	irrev.
$Na^{\oplus}$	−0.38	90	−0.75	90
+[2.2.1]	−0.44	90	−1.1	irrev.
$K^{\oplus}$	−0.43	80	−0.86	90
+[2.2.2]	−0.45	90	−1.1	irrev.
$nBu_4N^{\oplus}$ [b]	−0.48	100	−1.29	200

[a] $A^{2\ominus}$ = 3,5-$tBu_2C_6H_2$-1,2-$(O^{\ominus})_2$. [b] Determined by reduction of 3,5-di-*tert*-butyl-*o*-benzoquinone in DMF/$nBu_4N^{\oplus}ClO_4^{\ominus}$.

Both sets of data, the potentials $E^{(1)}_{1/2}$ (Table 1) and the radical anion coupling constants $a_{H,M}$ (Fig. 1), can be linearly correlated with the characteristic cation quantity charge/ionic radius[3,4]. After cryptand complexation or with the large cation tetra-*n*-butylammonium as counterion, the half-wave potentials for the catechol dianion

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and for the semiquinone radical anion in dimethylformamide (DMF), for example, approach -1.29 V (irreversible; presumably due to subsequent reaction) and -0.48 V (quasi-reversible, cf. Table 1; theoretical value for a reversible potential $\Delta E \approx 60$ mV), respectively. The ion-pair interactions detected by cyclic voltammetry or by ENDOR spectroscopy in the redox reaction (2) under the conditions chosen here are therefore reduced to an approximately negligible amount by addition of cryptand.

For the "naked" $MnO_4^{\ominus}$ anion with $K^{\oplus}$([18]crown-6) as counterion, the cyclic voltammogram in DMF affords a quasi-reversible ($\Delta E = 80$ mV) half-wave potential at -0.73 V versus SCE; this is shifted by more than 1 V relative to the value of $+0.32$ V[1] measured in aqueous solution versus the calomel electrode (SCE)! Compared to the $MnO_4^{\ominus}$ reduction in aqueous solution, in which the presumably initially (kinetically controlled) formed $HMnO_4^{\ominus}$ monoanion cannot be observed because of rapid subsequent reactions, the (thermodynamically determined) uptake of an electron to afford the nonprotonated $MnO_4^{2\ominus}$ dianion is therefore considerably handicapped in weakly solvating, organic solvents.

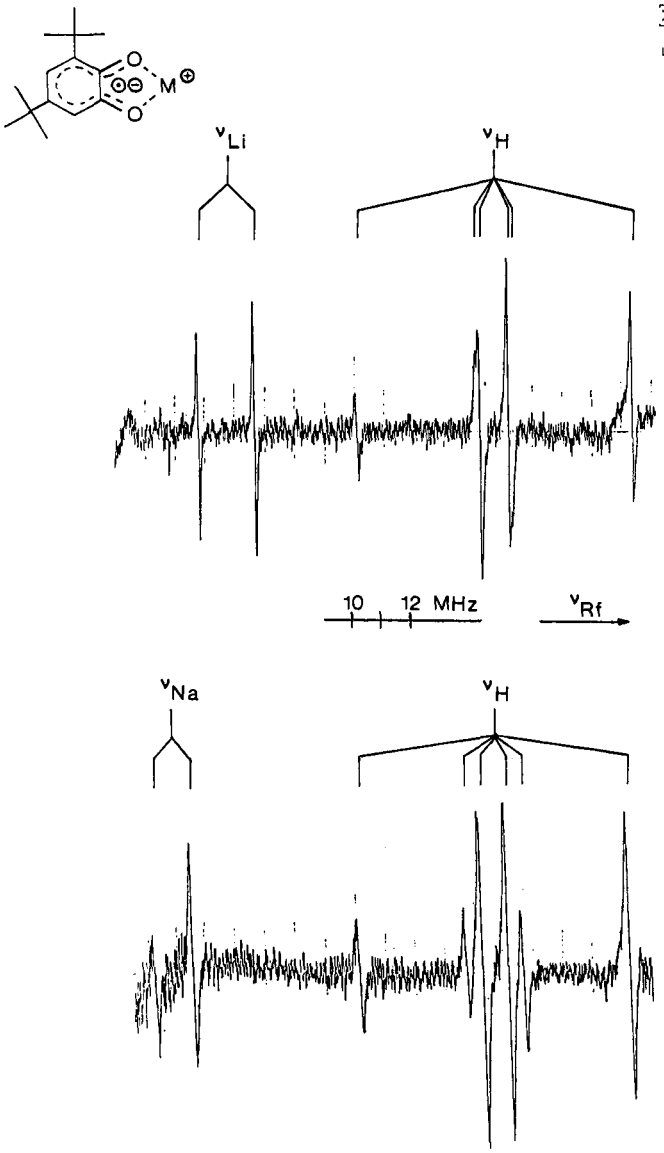

Fig. 1. ENDOR spectra of the Li (upper) and Na salts (lower) of 3,5-di-*tert*-butyl-*o*-benzosemiquinone radical anion at 190 K in tetrahydrofuran.

Under similar, aprotic conditions (Table 1), the half-wave potentials of other redox equilibria, e.g. the hyperoxide ion or the radical anions of cyano-substituted π-systems, were, in part, re-determined[3] in dimethylformamide and arranged in an electrochemical potential series (Fig. 2).

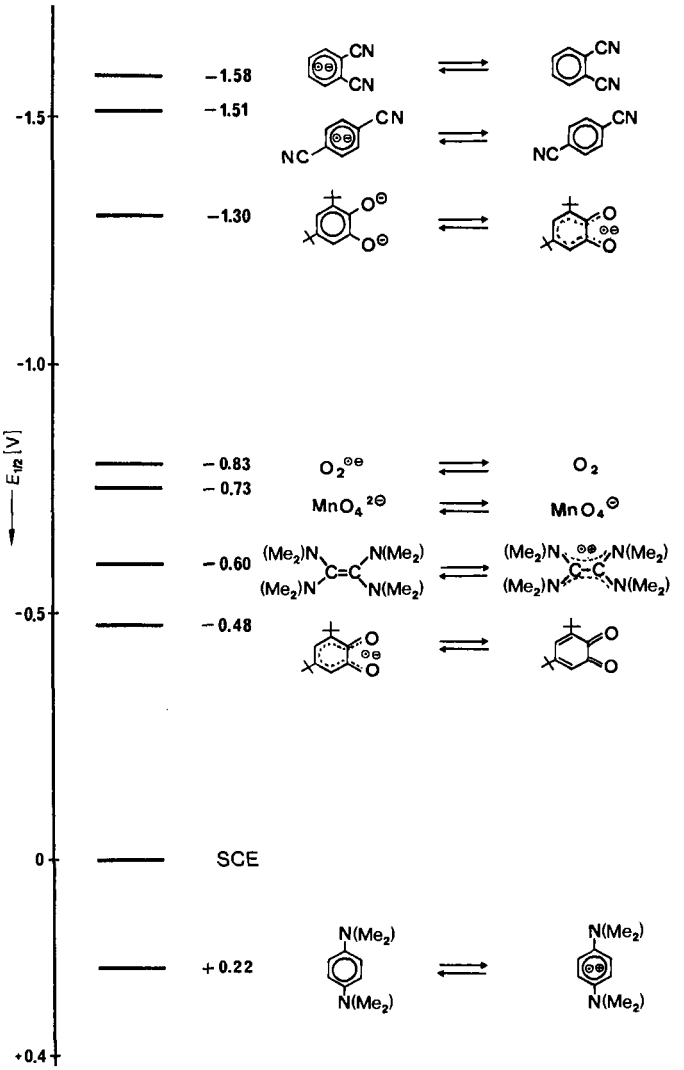

Fig. 2. Electrochemical potential series of redox systems in DMF/$R_4N^{\oplus}ClO_4^{\ominus}$ (0.1 M) at 298 K versus SCE.

Figure 2 indicates that $MnO_4^{\ominus}$ can indeed oxidize the dianion of 3,5-di-*tert*-butylcatechol, but not the semiquinone radical anion thus formed. Furthermore, electron-rich π systems like tetrakis(dimethylamino)ethene ($IE_1^{\gamma} = 5.95$ eV[5a]) or tetramethyl-*p*-phenylenediamine ($IE_1^{\gamma} = 6.75$ eV[5b]), which form isolable, stable radical cations such as Wursters' blue, are also unable to transfer an electron to $MnO_4^{\ominus}$ in aprotic solutions; traces of e.g. water are required to initiate the $MnO_4^{\ominus}$ reduction [cf. (1)], leading to precipitation of manganese dioxide[3]. In contrast, dicyano-substituted benzene radical anions—characterized by the disappearance of their ESR signals—are immediately discharged to the neutral compound. Deep green solutions of the $MnO_4^{2\ominus}$ dianion in DMF remain in the redox reaction with the hyperoxide radical anion[3].

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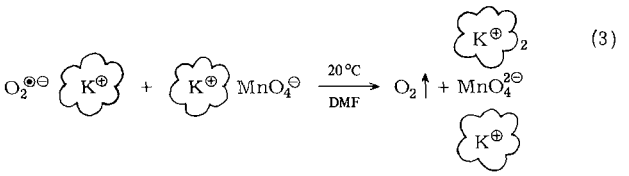

(3)

Many feasible electron transfers between thermodynamically controlled redox systems can be deduced from the electrochemical potential series (Fig. 2), such as the titration of Wursters' blue $[R_2NC_6H_4NR_2^{\odot\oplus}]I^{\ominus}$ with the electron-rich $(R_2N)_2C{=}C(NR_2)_2$ to the neutral compound $R_2NC_6H_4NR_2$ and the radical cation $(R_2N)_2C{=}C(NR_2)_2^{\odot\oplus}$, which can be followed by ESR spectroscopy[3].

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CAS Registry numbers:
$MnO_4^- \cdot K^+$, 7722-64-7; MnO_4^-, 14333-13-2; $n\text{-}Bu_4N^+ \cdot ClO_4^-$, 1923-70-2; 3,5-di-*tert*-butylpyrocatechol dianion dilithium salt, 61373-03-3; 3,5-di-*tert*-butylpyrocatechol dianion disodium salt, 61373-02-2; 3,5-di-*tert*-butylpyrocatechol dianion dipotassium salt, 89398-62-9; 3,5-di-*tert*-butyl-*o*-benzosemiquinone lithium salt, 4942-48-7; 3,5-di-*tert*-butyl-*o*-benzosemiquinone sodium salt, 54858-88-7; 3,5-di-*tert*-butyl-*o*-benzosemiquinone potassium salt, 4942-49-8; 3,5-di-*tert*-butylpyrocatechol dianion, 65767-24-0; 3,5-di-*tert*-butyl-*o*-benzosemiquinone, 34515-66-7; [2.2.2]cryptand, 23978-09-8; 3,5-di-*tert*-butyl-*o*-benzoquinone, 3383-21-9.

[1] a) Cf. e.g. Hollemann-Wiberg: *Lehrbuch der Anorganischen Chemie, 90th edit.*, de Gruyter, Berlin 1976, p. 204f., 908f.; b) cf. e.g. F. Vögtle, E. Weber, U. Elben, *Kontakte (Merck) 1980* (2), 36 and literature cited therein; c) G. W. Gokel, H. D. Durst, *Synthesis 1976*, 168.

[2] Cf. M. D. Stallings, M. M. Morrison, D. T. Sawyer, *Inorg. Chem. 20* (1981) 2655, 4257 and literature cited therein.

[3] D. Jaculi, Diplomarbeit, Universität Frankfurt 1983 and literature cited therein. For reactions of the hyperoxide radical anion cf. E. J. Nanni, M. D. Stallings, D. T. Sawyer, *J. Am. Chem. Soc. 102* (1980) 4481; or for reactions of cyano-substituted benzenes: P. H. Rieger, I. Bernal, W. H. Reinmuth, G. K. Fraenkel, *J. Am. Chem. Soc. 85* (1963) 683.

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[5] a) B. Cetinkaya, G. H. King, S. S. Krishnamurthy, M. F. Lappert, J. B. Pedley, *Chem. Commun. 1971*, 1370; b) cf. W. Kaim, H. Bock, *Chem. Ber. 111* (1978) 3843 and literature cited therein.

Preparation and Crystal Structure of $CuCo(CO)_4$: A Carbonylheterometal Complex Containing a Cu_4Co_4-Ring**

By *Peter Klüfers**

Structural investigations on compounds of the type $E[Co(CO)_4]_n$ in which $n \geq 2$ (E = Zn, Hg, In, Bi) have shown that in the crystalline state monomeric molecules with E–Co bonds are present in which E is of normal valence and fully coordinated[1]. For n = 1 (E = alkali metal, Tl^I), structural parameters are available for ionic compounds $E^{\oplus}[Co(CO)_4]^{\ominus}$ not having short E–Co contacts[2], and for $AgCo(CO)_4$ **2**, a compound with Ag–Co bonds in which coordinative saturation of the Ag atoms is reached in tetrameric molecules with a planar Ag_4Co_4 ring[3].

We have now been able to prepare the lighter homologue $CuCo(CO)_4$ **1** by reaction of $NaCo(CO)_4$ in tetrahydrofuran with a hydrochloric acid solution of CuCl (molar ratio 1:1) and to elucidate its structure[4].

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Orange colored, monoclinic crystals of **1** contain tetrameric molecules (C_2 symmetry). The sides of a planar, almost square arrangement of Cu atoms are bridged by $Co(CO)_4$ tetrahedra whose edges pointing towards the Cu atoms are greatly lengthened by the formation of Cu–Co bonds. In the Cu_4Co_4 ring thus formed, Co atoms project out oppositely from one another from the Cu_4-plane (48.5(1) and −68.3(1) pm). Two arrays of seven carbonyl groups, one above and one below the metallacycle, form two layers representing fragments of layers in a close packed structure; the two remaining CO groups of a molecule (CO′ groups) are located between these $(CO)_7$-layers (Figs. 1 and 2).

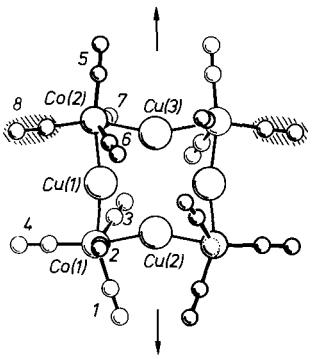

Fig. 1. Molecular structure of the bimetal complex **1** in the crystal. Atomic distances in the heavy-atom skeleton: Co(1)–Cu(1) 237.2(10), Co(1)–Cu(2) 236.0(3), Co(2)–Cu(1) 236.4(9), Co(2)–Cu(3) 236.5(7), Cu(1)–Cu(2) 273.1(4), Cu(1)–Cu(3) 270.3(4). Angles [°] in the Cu_4Co_4 ring at: Co(1) 69.65(6), Co(2) 70.55(4), Cu(1) 167.41(4), Cu(2) 158.07(6), Cu(3) 158.42(8). Bold- and thin-lined CO groups form densely packed layers above and below the Cu_4 plane, respectively. The two CO′ groups not incorporated in the close packing are shaded.

Related compounds with an eight-membered ring of alternately arranged transition- and d^{10}-elements are $[CdFe(CO)_4]_4 \cdot 2(CH_3)_2CO$ and $[(\eta^5\text{-}CH_3C_5H_4)Mn(CO)_2Hg]_4$ **3**[5]. Molecules containing a central Cu_4 unit are known for a series of organocopper(I) compounds, where the Cu–Cu distances are about 30 pm shorter than in **1**[6]. Mutual interaction between the metal atoms should have little if any influence on the molecular structure of organocopper(I) compounds[6], whereas bonding between the Hg atoms has been discussed in the case of the metallacycle **3**.

A comparison of the structure of **1** with that of the silver compound **2** reveals two outstanding differences: firstly, in **2** the metal framework is almost planar, while in **1** the CO atoms are not in the Cu_4 plane; secondly, the $Co(CO)_4$ groups in **2** deviate about 10° more from the tetrahedral structure than in **1**.

The crystal structures must be taken into consideration for an explanation of these effects, which are probably caused by the difference in size of the Cu and Ag atoms. In the structural chemistry of the tetracarbonylcobaltates $ECo(CO)_4$, two types of structure can be distinguished: 1) close packing of E + 4CO, with Co atoms in interstices when E is large; 2) close packing of CO groups alone, with Co and E in interstices when E is smaller[2].

The former type of structure is present in crystals of **2**, whereas the crystal structure of **1** can be derived from a strongly distorted, close packing of CO groups. The $(CO)_7$-fragments of close-packed layers formerly present in the molecule are part of close-packed CO planes in the crystal. These planes are distorted by CO′ groups which group pairwise at one position in the close arrangement (Fig. 2).

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Thus, the arrangement of ligands resulting from the nonplanarity of the metallacycle in **1** corresponds with the arrangement of the CO groups in the crystal structure. Presumably, therefore, the observed nonplanarity of the individual molecules, even if not brought about by the packing of the molecules in the crystals, is at least stabilized. A greater influence of the crystal structure on the molecular

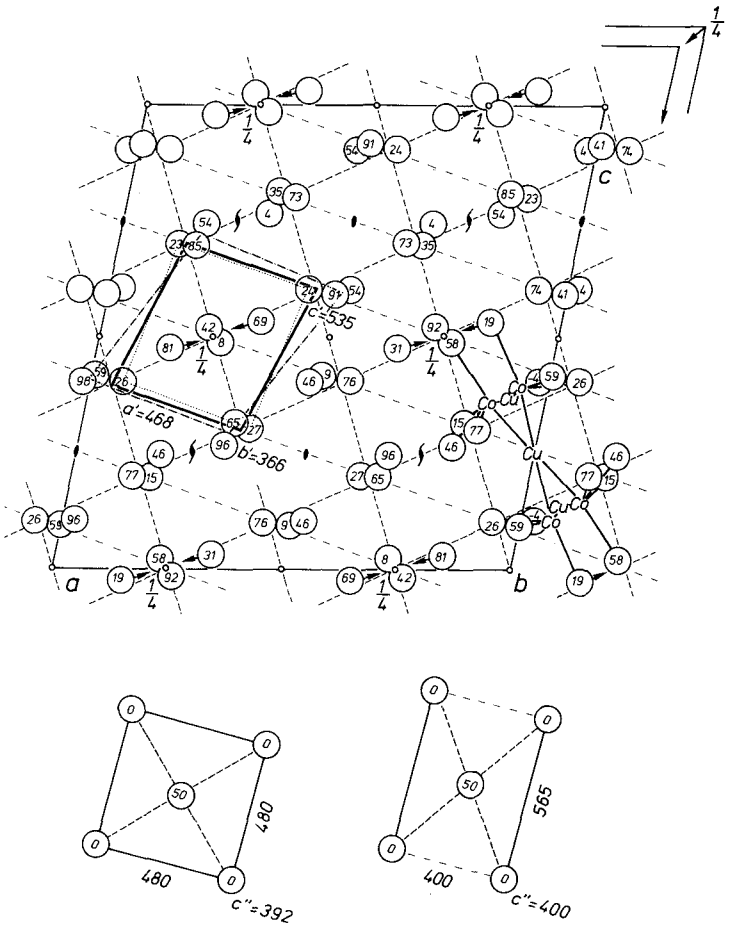

Fig. 2. Top: Crystal structure of **1**, projection on (010). Circles: CO groups, circles with arrows: CO′ groups, showing $y_{CO} \cdot 100$, $y_{CO} = 1/2(y_C + y_O)$. ----- Traces of densely packed layers, layers $(20\bar{1})$ contain the fragments of densely packed CO layers preformed in the molecules. ——, ····· Connecting lines between densely packed particles. —— Mean subunit in CO packing; $b' = b/3$. ·-·-·-·- 1CO+2CO′ subunit, frequency: 1 per unit length in [010]. ····· 2CO subunits, frequency: $2/b$. A complete molecule is indicated about $(0, y, 1/4)$.—Bottom: Measurements (in pm) of equal-volume cells idealized with the average subunit. Left: Tetragonal body-centered close packing, $c/a = \sqrt{2}/\sqrt{3}$, density of packing 0.698, projection on $(001)_{tetr.}$. Right: Cubic close packing, projection on $(01\bar{1})_{cub}$, tetragonal body-centered arrangement $\vec{c}'' = \frac{1}{2}(-\vec{a}_{2,cub} + \vec{a}_{3,cub})$.

structure is discussed for the denser crystal structure of **2** (V/Z [10^6 pm^3]: 169.3 in **1**, 168.6 in **2**). Hence, it is assumed[3] that striking molecular parameters in the neighborhood of the axial CO groups, namely pronounced widening of the $Co(CO)_4$ tetrahedral angle ($\sphericalangle C_{ax}-Co-C'_{ax} = 146.1°$) and unusual deviation of the Co–C–O angle from linearity (171.4°), are not to be considered as indicative of semibridging carbonyl groups, but should be explained in terms of packing effects only in the crystal. The present parameters for **1**, which, with the smaller Cu atom, does not facilitate formation of this type of structure, confirm this presumption ($\sphericalangle C_{ax}-Co-C'_{ax} = 136.7°$, $\sphericalangle Co-(C-O)_{ax} = 174.1°$).

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[2] P. Klüfers, *Z. Kristallogr. 162* (1983) 138; *ibid.*, in press.

[3] P. Klüfers, *Z. Kristallogr.*, in press.

[4] C_4CoCuO_4 ($M_r = 234.521$), C2/c, $Z = 16$, $a = 1578.8(5)$, $b = 1097.0(2)$, $c = 1598(5)$ pm, $\beta = 101.86(6)°$, $\rho_{calc} = 2.300$ g/cm^3; $Mo_{K\alpha}$ ($\omega - 4/3\theta$ scan), Enraf-Nonius CAD4, $+h \pm k \pm l$, $2° \leq \theta \leq 27°$, 6110 reflections, 2951 independent, 2022 with $|F| \geq 4\sigma(F)$, SHELX, with 183 refined parameters for all reflections $R = 0.071$, $R_w = 0.055$, for observed reflections only $R = 0.040$, $R_w = 0.051$. Maximum residual electron density 0.64 e/10^6 pm^3. Further details of the crystal structure investigation are obtainable on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2 on quoting the depository number CSD 50745, the names of the authors, and the journal citation.

[5] Cd: R. D. Ernst, T. J. Marks, J. A. Ibers, *J. Am. Chem. Soc. 99* (1977) 2091; Hg: W. Gäde, E. Weiss, *Angew. Chem. 93* (1981) 796; *Angew. Chem. Int. Ed. Engl. 20* (1981) 803.

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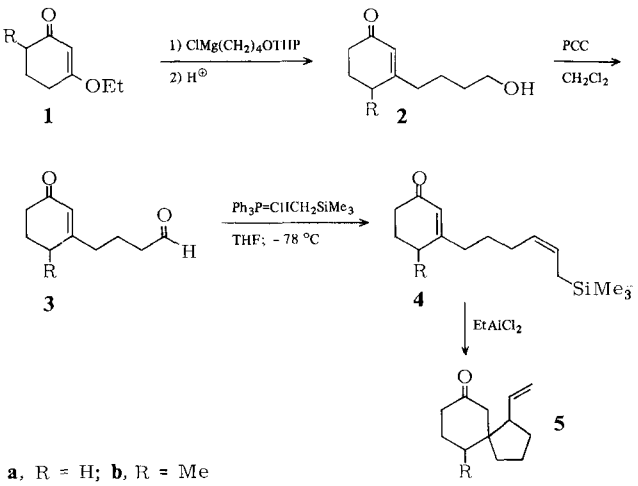
Diastereoselective Synthesis of Spiro[4.5]decanones by Intramolecular Sakurai Reactions**

By *Dieter Schinzer**

The syntheses of complex ring systems, e.g. natural products like lubimin or α-acoradiene which contain the spiro[4.5]decane system, have recently attracted the attention of synthetic chemists[1,2]. We have investigated a new stereoselective route to functionalized spiroketones (**4**→**5**) using Lewis acid-catalyzed cyclizations of allylsilanes **4**, which are readily accessible from 3-ethoxy-2-cyclohexenones **1** as shown in Scheme 1.



Scheme 1. THP = tetrahydropyranyl; PCC = pyridinium chlorochromate.

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Of decisive importance for the cyclization of compounds **4** is the choice of Lewis acid: BF_3 and $SnCl_4$, for instance, lead only to protodesilylation, while decomposition occurs with $TiCl_4$. With ethylaluminum dichloride, on the other hand, an intramolecular Sakurai reaction takes place[3], leading to the desired spiroketones **5** in good yields (Table 1)[4].

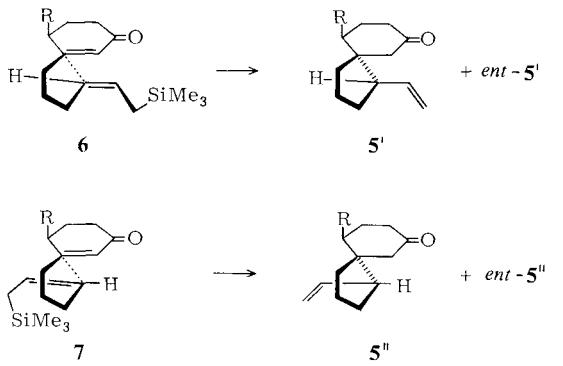

Table 1. Conditions for the conversion **4**→**5**, ratio of the diastereomers **5'** and **5''**, and yields of **5** [a].

4	Conditions	5':5''	Yield [%]
a	CH_2Cl_2, −78°C	2:1	85
a	toluene, 0°C	3:1	77
a	toluene, −78°C	7:1	72
b	toluene, 0°C	5:1 [b]	75
b	toluene, −78°C	7.5:1	70

[a] General procedure, e.g. for **5a**: To a solution of 165 mg (0.66 mmol) **4a** in 30 mL anhydrous toluene is added 0.1 mL (1.1 equiv) ethylaluminum dichloride at 0°C. The mixture is stirred for 30 min at 0°C, treated with 10 mL ice-water, and the phases are separated and extracted twice with 30 mL ether. The combined organic phases are dried over sodium sulfate and evaporated down. Kugelrohr distillation (60°C, 0.1 mbar) affords 90.5 mg (77%) **5a** (**5a'**:**5a''** = 3:1). Physical data of **5a'**: IR (film): ν = 1715 (s), 920 (m) cm^{-1}; ^{1}H-NMR (90 MHz, $CDCl_3$): δ = 1.1–2.5 (m, 15H), 5.1 (m, 2H), 5.7 (m, 1H); ^{13}C-NMR (20.15 MHz): δ = 212.4 (s), 138.5 (d), 116.4 (t), 54.4 (d), 50.2 (s), 47.0 (t), 41.2 (t), 35.8 (t), 29.7 (t), 23.5 (t), 21.4 (t). [b] In addition to the two diastereomers shown, a third occurs (5:1:0.5) of unknown structure.

Interestingly, depending on the temperature and solvent the reaction proceeds diastereoselectively (Table 1), favoring a synclinal transition state **6**. The other diastereomer is formed via an antiperiplanar transition state **7**. Assignment of the configurations of the products followed from known ^{13}C-NMR[5] and ^{1}H-NMR data of the synthesized dimethoxyketals and from NOE experiments[6]. The stereochemistry of the methyl group in **5b** could not be clarified with certainty.

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[4] All new compounds were characterized spectroscopically and gave correct elemental analyses. The spiroketones have a pleasant fruity smell.
[5] W. Oppolzer, L. Garrichon, T. G. C. Bird, *Helv. Chim. Acta 64* (1981) 186.
[6] I wish to thank Dr. *V. Wray*, Gesellschaft für Biotechnologische Forschung (GBF), Braunschweig-Stöckheim, for carrying out the NOE experiments.

4*H*-1,4-Oxazocine, a Planar, Diatropic 10π-Dihetero[8]annulene?**

By *Bernhard Zipperer, Dieter Hunkler, Hans Fritz, Grety Rihs,* and *Horst Prinzbach**

In the chemistry of π-electron-rich heteroannulenes[1] such as e.g. 1,4-diheterocines **2**, iso-π-electronic with the 10π-cyclooctatetraene dianion **1**, the analysis of the influence of the heteroatoms on the molecular properties remains a topic of current interest[2]. For the 1,4-dihydro-1,4-diazocine **3** the following relationship between *N*-substitution and molecular structure has been observed:

For R=H (donor) **3** is planar with a delocalized 10π system, and for R=SO_2R (acceptor) it is twisted with a localized π-system[3,4]. We show here that a similar relationship between *N*-substitution and molecular structure exists in the 4*H*-1,4-oxazocine framework **4** with the O atom having a lower tendency to n-electron delocalization[2].

1 **2** **3** **4**

X-ray structure analysis (Fig. 1, top)[6] of the recently described *N*-tosyl-1,4-oxazocine **4a**[5] confirms the nonplanar, highly irregular conformation with considerable torsion around the C=C bonds—as expected from the NMR data. It was initially attempted to synthesize donor-substituted derivatives and the parent compound **4b** via the route previously worked out for **4a** (**5**→**6**→**7**→**8**→**4**). **5** actually adds *N*-nucleophiles such as methylamine, aniline, benzylamine, and sodium azide (methanol, $ZnSO_4$, room temperature, 1-2 d)—without side reactions, e.g. S_N2' substitution—to the allylic epoxide position to afford the conduritol derivatives **6b-6e** (80—95%, $J_{1,2}$ = 2-2.5, $J_{2,3}$ = 5.5-6.5, $J_{6,1}$ = 4.5-5.5 Hz, with high 1e,2a,3a,6e-contributions)[7]. However, reaction of **6b-6d** with bases such as diazabicycloundecene (DBU) and potassium *tert*-butoxide in tetrahydrofuran (THF) or with sodium methoxide in methanol (−30 to +50°C)[5] leads under various conditions only to rapid polymerization.

Problems also arose in the attempt to prepare the *cis*-oxaaza-bis-σ-homobenzene **8b** (and from this **4b**) from the epoxy-*trans*-azido alcohol **7e**, isolated in high yield via **6e** (KO*t*Bu, THF, −10°C, 5 min, 90%, $J_{2,3}$ = 2 Hz) and triphenylphosphane[8]. The pure, colorless, powder-like iminophosphorane **9** (86%) precipitates from anhydrous ether. Despite the propitious e,e-position of the OH/NP(C_6H_5)$_3$ groups for *trans*-cyclization to a five-membered ring, the conversion into **8b** proceeds so slowly that considerable decomposition (from **9** and **8b/4b**, the only product identified was the amine **7f**) is unavoidable; the thermally labile parent compound **4b**—even at 20°C, **8b** is not detectable directly (^{1}H-NMR, TLC)—can be separated by chromatography only with high losses.

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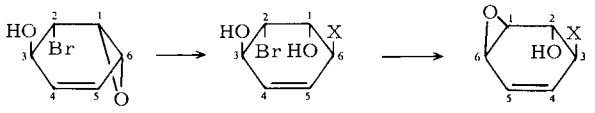
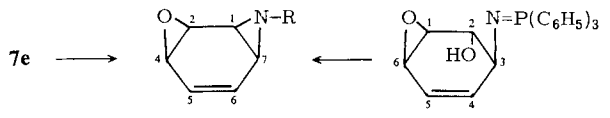
After optimization of the route to **4a**[5], **4b** as well as the derivatives **4c-4i** were prepared via the anion **10** generated by amide-cleavage (K/NH_3, $-33\,^{\circ}C$, orange-yellow powder; extracted with DMSO)[3]. Within the analytical limits (^1H-NMR, 400 MHz), **10** is protonated (deuterated) exclusively to **4b** (**4c**) and **4b**, **4c** do not tautomerize in the presence of strong bases. **4b** crystallizes from ether ($-20\,^{\circ}C$) as pale yellow platelets (m.p. = 32 °C, 65%), which rapidly deliquesce in air and are thermally labile. Like **4b**, **4d-4f** are unstable and, hence, can only be characterized in solution (NMR). The dimethylcarboxamide **4h** and the urethane **4i** are more stable and can be purified by chromatography (75–80%), but not crystallized. This was eventually achieved for the trimethoxybenzyl derivative **4g** (70%, colorless platelets, m.p. = 88-90 °C (decomp.), whose crystals were suitable for X-ray structure analysis.



5 **6** **7**

6,7	a	b	c
X	NHTos	$NHCH_3$	NHC_6H_5

	d	e	f
X	$NHCH_2C_6H_5$	N_3	NH_2



8a, R = Tos
8b, R = H

9

4 **10**

	a	b	c	d	e	f	g
R	Tos	H	D	CH_3	CH_2CH_2CN	$CH_2C_6H_5$	$CH_2C_6H_2(OCH_3)_3$

	h	i
R	$CON(CH_3)_2$	CO_2CH_3

The parent compound **4b**, the anion **10**, and the alkyl derivatives **4d-4g**—less typically **4h**, but not the **4a**-analogous **4i** (N–CO rotation is hindered at 30 °C)—exhibit in the ^1H- and ^{13}C-NMR spectra chemical shifts and particularly $J_{6,7}$- and $^3J_{C,H}$-couplings through the carbon-heteroatom bonds (exemplified in Table 1 with **4a**, **4b**, **4g** and **4i**), which are clearly different from those of the nonplanar **4a** and which make planar conformations probable.

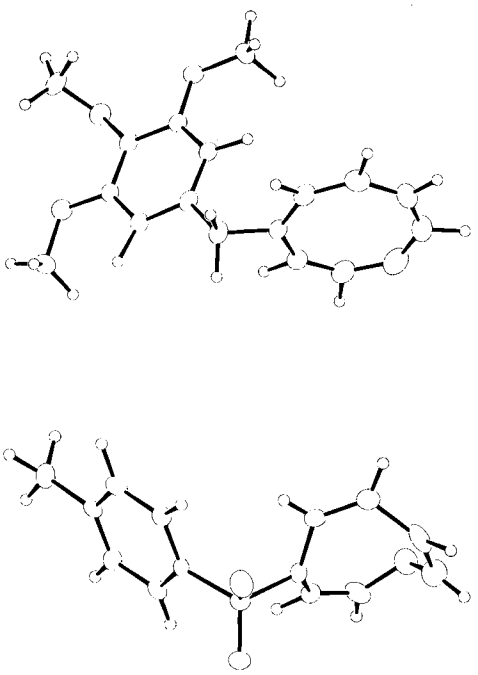


Fig. 1. Molecular structures of **4a** (above) and **4g** (below) in the crystal [6]. Important bond lengths [Å] of **4a** (**4g**): O1-C2 1.362 (1.338), C2-C3 1.293 (1.312), C3-N4 1.421 (1.369), N4-C5 1.412 (1.381), C5-C6 1.328 (1.360), C6-C7 1.527 (1.431), C7-C8 1.296 (1.314), C8-O1 1.385(1.333).

For **4g** a planar molecular structure (average deviation from the ideal plane 0.021 Å; average bond angle in the eight membered ring 135.5°) with a marked decrease in bond length alternation is ascertained (Fig. 1, below)[6]. In contrast to **4a**, which has pyramidal coordination at N4, the substituents at N4 in **4g** are practically coplanar; this satisfies the requirement for efficient n-electron delocalization. Following the arguments presented for **3**[3,4], we interpret these differences in structure and electron distribution, which go parallel with the acceptor or donor character of the *N*-substituents, as proof that cyclic 10π-electron delocalization is responsible, inter alia, for the planarity and that, in consequence, the 4*H*-1,4-oxazocine and its *N*-alkyl derivatives are diatropic[9].

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Table 1. $^1H(^{13}C)$-NMR data of **4a**, **4b**, **4g**, and **4i** ($CDCl_3$, 400 (100.6) MHz, ca. 30 °C).

	Chemical shifts (δ values)						$^3J_{H,H}$ [Hz]				$^3J_{C,H}$ [Hz]			
	2-H (c)	3-H (C)	5-H (C)	6-H (C)	7-H (C)	8-H (C)	$J_{2,3}$	$J_{5,6}$	$J_{6,7}$	$J_{7,8}$	$J_{2,8}$	$J_{3,5}$	$J_{5,3}$	$J_{8,2}$
4a	6.23 (129.0)	6.20 (105.2)	6.74 (121.3)	5.54 (109.4)	5.21 (105.5)	6.38 (144.4)	7.5	10	7	7.5	5.5	4.3	4	5.0
4b	6.51 (117.2)	5.82 (100.2)	6.57 (117.7)	5.35 (90.1)	5.61 (95.7)	7.06 (131.8)	8.0	10.5	10.5	8.5	8.0	9.0	9.5	8.5
4g	6.50 (117.6)	5.72 (105.2)	6.59 (123.1)	5.36 (90.7)	5.62 (96.4)	7.01 (131.8)	8.0	11	10.5	8.0	9.5	7.5	6.5	8.5
4i	6.06 (131.4)	6.13 (109.6)	6.57 (125.3)	5.40 (110.4)	5.33 (108.9)	6.36 (141.8)	6.0	9.5	6.5	7	<5	≈3	<5	(≈5?)

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$[Cu_{12}S_8]^{4\ominus}$: A Closed Binary Copper(I) Sulfide Cage with Cuboctahedral Metal and Cubic Sulfur Arrangements**

By *Peter Betz, Bernt Krebs,* and *Gerald Henkel**

Copper is frequently encountered in biological systems, and copper-sulfur bonds have been detected in some metalloproteins[1].

Among the polynuclear copper(I) complexes with complete sulfur coordination and known structure are compounds with Cu_4S_6, Cu_4S_8, or Cu_8S_{12} frameworks which contain trigonally coordinated metal atoms[2]. Distorted, tetrahedral coordination of sulfur occurs, e.g., in the tetranuclear thiourea complex $[Cu_4(tu)_9]^{4\oplus}$ in addition to trigonal coordination[3]. Two pentanuclear compounds are also known in which both trigonal and linear coordination of sulfur are observed[4]. In all these compounds the sulfur atoms are a functional part of thiolates, of unsaturated 1,1- or 1,2-dithiolates (dithiolenes), or of dithiosquarates or thiourea; the tetranuclear Cu_4S_6 moiety is preferentially formed by thiolates and thiourea, whereas the octanuclear Cu_8S_{12} moiety achieves its maximum stability with 1,1- and 1,2-dithiolenes, and dithiosquarates. Di-, tri-, hexa-, and heptanuclear Cu^I–S complexes are not yet known[10].

In the course of systematic investigations of polynuclear metal-thiolate and metal-sulfide-thiolate complexes, we have isolated and structurally characterized the novel hexanuclear cluster $[Cu_6(S_4)_3(S_5)]^{2\ominus}$[5], besides the tetranuclear clusters $[Cu_4(S_4)_3]^{2\ominus}$, $[Cu_4(S_4)_2(S_5)]^{2\ominus}$, and $[Cu_4(S_4)(S_5)_2]^{2\ominus}$ from the copper/sulfur/ethanethiolate reaction system[6]. Under suitable conditions, the trinuclear cluster $[Cu_3(S_4)_3]^{3\ominus}$ and the tetranuclear, mixed-valent anion $[Cu^I_3Cu^{II}(S_4)_3]^{\ominus}$ could be trapped in a $[Ph_4P]_2[Cu_4(S_4)_3]$ matrix[7].

Formation of the stable tetra- and pentasulfido complexes can be avoided by using Li_2S instead of elemental sulfur. We report here the novel anion $[Cu_{12}S_8]^{4\ominus}$ **1**, which with twelve metal atoms in a cuboctahedral arrangement is particularly interesting not only as the largest Cu–S cluster but also as the first isolated Cu^I–S complex with exclusively monosulfido ligands and also because of its closed cage structure. $[Cu_{12}S_8]^{4\ominus}$ is formed in the reaction of $CuCl_2\cdot 2H_2O$ with $EtS^{\ominus}$ (threefold excess) in methanol, followed by cooling to −78 °C and addition of Li_2S. Upon slowly warming the mixture in the presence of Ph_4PBr, an orange, finely crystalline precipitate of $[Ph_4P]_4[Cu_{12}S_8]$ **2** is formed, which can be obtained as wine-red needles from dimethylformamide.

Apart form $Ph_4P^{\oplus}$ cations, crystals of **2** contain discrete $[Cu_{12}S_8]^{4\ominus}$ anions with ideal O_h symmetry, whose centroids occupy crystallographic centers of inversion. The structure of the tetraanion **1** is shown in Figure 1. The closed metal-sulfur cluster has approximately the shape of a cube whose corners are defined by sulfur atoms, whereas the midpoints of the edges are occupied by copper atoms. Thus this structure represents an inverse copper-sulfur arrangement with respect to the Cu_8S_{12} centers of the octanuclear Cu^I dithiolene complexes.

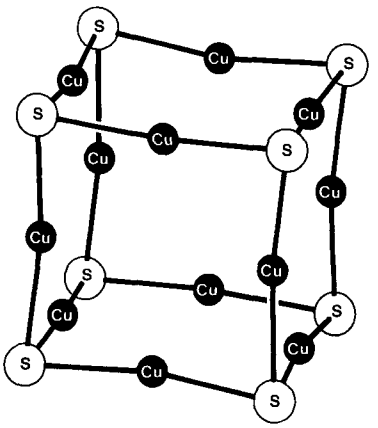

Fig. 1. Structure of the $[Cu_{12}S_8]^{4\ominus}$ cluster **1** in the crystal of salt **2** [monoclinic, $P2_1/n$, $a=13.968(12)$, $b=25.710(23)$, $c=12.681(9)$ Å, $\beta=91.17(7)°$, $Z=2$; Syntex-$P2_1$, four-circle diffractometer, $Mo_{K\alpha}$ radiation, graphite monochromator, scintillation counter, 2θ-θ scan, $2\theta_{max}=48°$, $T=-130$ °C, 7196 symmetry-independent reflections, 4917 of which with $I>1.96\sigma(I)$; $R=0.046$, $R_w=0.037$]. Range of distances: Cu...Cu 2.774(1) to 2.950(1), Cu–S 2.156(2) to 2.179(2) Å; range of angles: S–Cu–S 166.87(7) to 170.89(7), Cu–S–Cu 79.75(6) to 86.08(6)°. Further details on the crystal structure analysis can be obtained from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, by quoting the depository number CSD 50753, the names of the authors, and the journal citation.

The metal framework of the $[Cu_{12}S_8]^{4\ominus}$ cluster derives from the cubic closest sphere packing of elemental copper, and as a cuboctahedron represents the section of twelve metal atoms around a non-occupied center (cf. Fig. 2). The Cu–Cu distances in **1** range between 2.774(1) and 2.950(1) Å, and the average value (2.845 Å) is ca. 0.3 Å larger than the corresponding value in metallic copper.

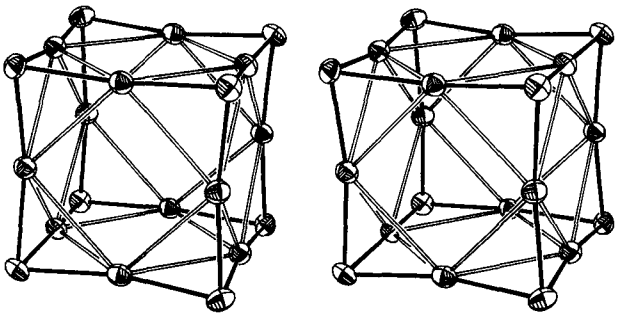

Fig. 2. Stereoscopic projection of the $[Cu_{12}S_8]^{4\ominus}$ cluster **1** with vibrational ellipsoids (50% probability, −130 °C) and sketched metal cuboctahedron.

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The copper atoms are displaced slightly from their ideal positions at the midpoints of the edges of the S_8 cube towards the (unoccupied) center; the S–Cu–S fragments are therefore not linear but exhibit angles between 166.87(7) and 170.89(7)° at the Cu atom with bond lengths between 2.156(2) and 2.179(2) Å (average 2.163 Å).

The distorted linear coordination of sulfur observed in **2** is also realized in the highly condensed compounds KCuS (Cu–S 2.155 Å) and $CsCu_3S_2$ (Cu–S 2.166 Å)[8]. However, this is rather the exception in the Cu^IS clusters isolated in which trigonal-planar or tetrahedral sulfur coordination dominates. In addition to trigonal CuS_3 moieties, further examples of distorted linear CuS_2 coordination are found only in the pentanuclear anions $[Cu_5(S\mathit{t}Bu)_6]^{\ominus}$ and $[Cu_5(SPh_7)]^{2\ominus}$[4].

In **1** the S atoms are centered above the triangular faces of the metal cuboctahedron and form μ_3-S bridges with Cu–S–Cu angles between 79.75(6) and 86.08(6)°. Although $(\mu_3\text{-S})M_3$ moieties are frequently observed as basic elements of the $[M_4S_4]$ cubane structure in transition-metal-sulfur chemistry (cf. e.g. [9]), $[Cu_{12}S_8]^{4\ominus}$ is the first complex whose metal centers are coordinated exclusively by μ_3-S ligands. The IR spectrum of **2** exhibits a strong Cu–S stretching frequency at 382 cm^{-1}.

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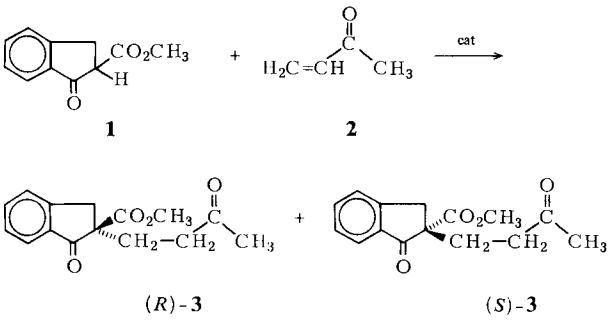
Enantioselective Michael Additions with Optically Active Co^{II}/Diamine Catalysts**

By *Henri Brunner** and *Benedikt Hammer*

CC Bond formations via Michael addition are catalyzed by bases[1]. The use of optically active amines[2] or of optically active crown ethers and bases[3] leads to different degrees of optical induction. 1,3-Dicarbonyl compounds can be preparatively alkylated with α,β-unsaturated systems in particularly high yields if transition metal catalysts such as $Ni(acac)_2$[4] are employed instead of bases.

We have now developed $Co(acac)_2$/(nn), (nn)=(+)- or



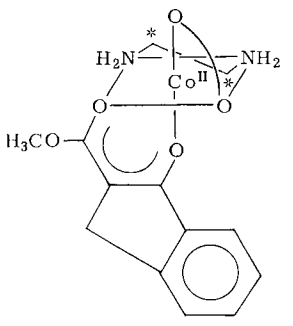
(−)-1,2-diphenyl-1,2-ethanediamine, a catalyst system for the enantioselective addition of methyl vinyl ketone **2** to cyclic and open-chain 1,3-dicarbonyl compounds. The optical inductions are, however, markedly dependent on the structure of the CH-active components and for methyl 1-oxo-2-indanecarboxylate **1** reach 66% *ee*.

Treatment of a red-violet solution of $Co(acac)_2$ in toluene with one equivalent of the ligand (nn) results in formation of the red, octahedral Co^{II} complex $[Co(acac)_2(nn)]$, which can be detected as the molecular ion in the mass spectrum (field desorption from toluene). 3 Mol-% of this complex in toluene catalyze the addition of **2** to **1**. The Michael adduct **3** is obtained in 79% chemical yield and 21.3% *ee* after stirring for 40 h at +20°C. At constant chemical yield the optical induction increases continuously with decreasing temperature (Table 1, nos. 3–9) until at −50°C (64 h) a value of 66% *ee* is reached. At lower temperatures the reaction is too sluggish.

Compared to the complex $[Co(acac)_2\{(-)\text{-(nn)}\}]$, the free amine (−)-(nn) is a poorly effective and weakly inductive catalyst (no. 2). In contrast to the complex, which predominantly induces the (*S*)-configuration in the product, the free amine leads preferentially to the (*R*)-configuration. Use of excess (+)-(nn) (no. 12) causes a drastic reduction in the optical induction (Table 1).

In the reaction of methyl vinyl ketone **2** with ethyl 2-methylacetoacetate as CH-acidic component (nos. 13–14) in the presence of the catalyst system $Co(acac)_2$/(nn) at room temperature only 4.5% *ee* (0°C: 2.2%) is obtained. Because of the distillative work-up, chemical yields of the Michael adducts from ethyl 2-methylacetoacetate and **2** are a little lower than for **3**, which after concentration is separated from the catalyst by shaking with dil. hydrochloric acid and chromatography (silica gel).

The (*S,S*)-configuration of the ligand (+)-(nn)[5] gives rise to the λ-conformation in the Co(nn) five-membered ring, as shown in **4**. At the Co atom two methyl 1-oxo-2-indanecarboxylate anions and an (nn) ligand lead to an octahedral complex with Δ- or Λ-configuration. Complex **4**



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[**] Asymmetric Catalysis Part 18. This work was supported by the Deutsche Forschungsgemeinschaft and by BASF AG.—Part 17: [1].

Table 1. Co^{II}-catalyzed Michael addition of 400 mg (2.1 mmol) methyl 1-oxo-2-indanecarboxylate **1** to 0.6 mL (7.4 mmol) methyl vinyl ketone **2** in 30 mL toluene.

No.	Complex	Ligand	Molar ratio 1 : Co : Lig.	Reaction conditions	3 Yield [%]	*ee* [%]
1	$Co(acac)_2$	—	35.4 : 1 : —	+20°C, 40 h	98	—
2	—	(−)-(nn)	21.2 : — : 1	+20°C, 18 h	18	5.8 (*R*) [a]
3	$Co(acac)_2$	(+)-(nn)	30.2 : 1 : 1.07	+20°C, 40 h	72	21.3 (*R*) [a]
4	$Co(acac)_2$	(+)-(nn)	27.3 : 1 : 1.01	0°C, 39 h	83	28.2 (*R*) [a]
5	$Co(acac)_2$	(+)-(nn)	28.5 : 1 : 1.01	−10°C, 40 h	78	34.7 (*R*) [a]
6	$Co(acac)_2$	(+)-(nn)	16.4 : 1 : 1.02	−20°C, 65 h	74	39.4 (*R*) [a]
7	$Co(acac)_2$	(+)-(nn)	21.2 : 1 : 0.99	−30°C, 65 h	78	48.5 (*R*) [a]
8	$Co(acac)_2$	(+)-(nn)	17.9 : 1 : 1.0	−40°C, 62 h	74	56.9 (*R*) [a]
9	$Co(acac)_2$	(+)-(nn)	21.6 : 1 : 0.99	−50°C, 64 h	50	66 (*R*) [a]
10	$Co(acac)_2[(-)-(nn)]$	—	34.0 : 1 : —	−20°C, 65 h	79	37.2 (*S*) [a]
11	$Co(acac)_2[(-)-(nn)]$	—	36.2 : 1 : —	−40°C, 62 h	74	58.3 (*S*) [a]
12	$Co(acac)_2$	(+)-(nn)	32.8 : 1 : 3.60	−20°C, 43 h	71	16.6 (*R*) [a]
13	$Co(acac)_2$	(+)-(nn)	191 [b] : 1 : 1.01	+20°C, 41 h	62	4.5 (*S*) [c]
14	$Co(acac)_2$	(+)-(nn)	145 [b] : 1 : 1.05	0°C, 64 h	46	2.2 (*S*) [c]

[a] Relative to *S*-**3a**, $[\alpha]_{578}$ −77.0 ($c=2$, benzene) [2c]. [b] Substrate ethyl 2-methylacetoacetate. [c] Relative to $[\alpha]_D$ −9.6 ($c=1.29$, chloroform) [7].

(one of the two ester ligands is sketched as $\overset{\frown}{OO}$ and the phenyl groups are not shown) has the Δ-configuration. Consistent with the results of conformational analyses of corresponding Co^{III} complexes[6], this Δ-configuration for a given λ-conformation of the Co(nn) five-membered ring is thermodynamically stabler than the Λ-configuration.

Starting from the Δ(λ)-form of **4**, one obtains (*R*)-**3** if it is assumed that the keto-carbonyl group occupies an axial, and the ester carbonyl group an equatorial, position and that in addition the methyl vinyl ketone **2** is directed to the *si*-side of the complexed substrate via a hydrogen bond from the keto oxygen to one of the NH groups. This model accounts for the low optical induction for ethyl 2-methylacetoacetate in terms of a reduced axial/equatorial selectivity of ester and keto-carbonyl groups relative to **1**. The optical inductions attained with (nn)=(+)- and (−)-1,2-diphenyl-1,2-ethanediamine have not yet been achieved with (−)-1,2-diaminocyclohexane and (−)-3-phenyl-1,2-propanediamine Co^{II} complexes.

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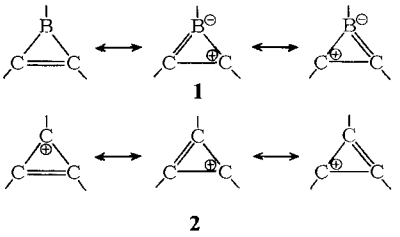
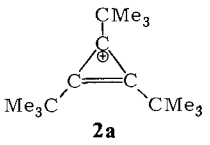
1-*tert*-Butylborirenes**

By *Christine Pues* and *Armin Berndt**

Borirenes **1** are the simplest borarenes isoelectronic with cyclopropenylium ions[1]. Attempts to synthesize compounds **1** remained unsuccessful[2,3] until introduction of sterically demanding substituents recently enabled the preparation of the first derivatives[4-6,10].

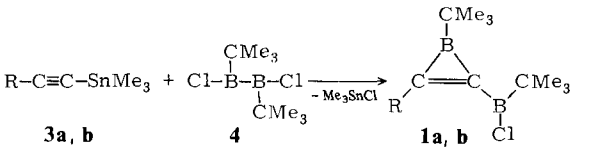




2a

We have now found that the 1-*tert*-butylborirenes **1a**, **b** are accessible in almost quantitative crude yields from the trimethylstannylalkynes **3** and 1,2-di-*tert*-butyl-1,2-dichlorodiborane(4) **4**.

The structures of **1a** and **1b** are consistent with the mass spectra and the ^1H-, ^{13}C- and ^{11}B-NMR data[7]. As was to be expected from the resonance structures of **1**, the B atom of the three-membered ring in **1a** and in **1b** is, in each case, strongly shielded owing to its relatively high π-electron density ($\delta=43$ and 49 compared to $\delta=81$ in boriranes[8]), while the C atoms are markedly deshielded



3a, b **4** **1a, b**

a, R = CMe_3; **b**, R = $SnMe_3$

($\delta=184.3$ and 186.6 in **1a**, 184.8 and 215.3[9] in **1b**). The ring C-atoms of compound **2a**, which is comparable to **1a**, have a chemical shift of $\delta=181.6$. The shielding of the cyclic boron atom in **1a** of 38 ppm compared to that in boriranes is markedly greater than the corresponding shielding of 31 ppm in **1d** ($\delta^{11}B\approx27$)[4] compared to that in dimethylbis(trimethylsilyl)aminoborane[11] ($\delta^{11}B=57.7$)[12]. We conclude, therefore, that the electron gap at the boron in **1d** not only interacts with the π-electrons of the three-membered ring but also with the electron pair at the nitrogen.

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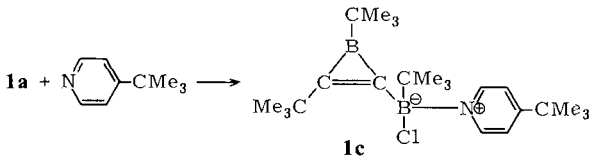

1c

1a reacts with 4-*tert*-butylpyridine to give a crystalline adduct **1c**, whose structure is proven by ^{1}H-, ^{13}C-, and ^{11}B-NMR spectra[7]. The addition of the pyridine at the exocyclic B atom follows from the relatively small change in the shift of the ring B-atom compared to that in **1a** ($\delta = 47$ compared to 43). Confirmation of the exocyclic addition is provided by the chemical shifts of the ring C-atoms ($\delta = 182.9$ and 193.1), which are similar to those in **1a**. All attempts to prepare crystals of **1c** for an X-ray structure analysis, to check the calculated[1b,c] bond lengths in borirenes, have so far failed.

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[5] No ^{11}B-shift has been quoted for the 2,3-di-*tert*-butyl-1-methylborirene **1e** which was obtained together with other compounds [6]; the ^{13}C-shift of the skeletal C-atoms ($\delta = 127-133$) is out of the region characteristic for borirenes (see text) [10].

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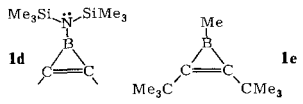


1d **1e**

[7] **1a**: colorless liquid, b.p. 68°C/2 torr; ^{1}H-NMR (100 MHz, $CDCl_3$): $\delta = 1.17$, 1.09, 1.01 (s, each 9H, *t*Bu); ^{13}C-NMR (100 MHz, $CDCl_3$): $\delta = 186.6$, 184.3 (s, each 1C, C=C, −30°C); 29.3, 28.9, 27.5 (q, each 3C, *t*Bu), 34.8 (s, 1C, CMe_3), 25.5, 18.0 (s, each 1C, CMe_3, −30°C); ^{11}B-NMR (32 MHz, $CDCl_3$): $\delta = 72$ (1B, BCl), 43 (1B, BC_3); IR (film): $\tilde{\nu} = 1680$ cm^{-1}; MS (intensities [%] in the molecular ion region (*m/z* 250–255): exp. 3.74, 40.85, 100, 22.07, 34.09, 4.8; calc. 4.8, 42.95, 100, 29.26, 33.24, 5.03.—**1b**: yellow liquid; b.p. 60°C/10^{-3} torr; ^{1}H-NMR: $\delta = 1.13$, 1.01 (s, each 9H, *t*Bu), 0.31 (s, 9H, $SnMe_3$); ^{13}C-NMR: $\delta = 215.3$, 183.8 (s, each 1C, C=C, −35°C); 28.9, 27.5 (s, each 3C, *t*Bu), 25.2, 18.4 (s, each 1C, CMe_3, −35°C), −8.9 (s, 3C, $SnMe_3$), ^{11}B-NMR: $\delta = 73$ (1B, BCl), 49.0 (1B, BC_3); IR (film): $\tilde{\nu} = 1620$ cm^{-1}.—**1c**: white solid; ^{1}H-NMR: $\delta = 9.16$ (m, 2H, *ortho*), 7.53 (m, 2H, *meta*), 1.35, 1.17, 1.16, 0.7 (s, each 9H, *t*Bu); ^{13}C-NMR: $\delta = 193.1$, 182.9 (s, each 1C, CBC, −30°C), 166.1 (s, 1C, *para*), 145.8 (d, 2C, *ortho*), 121.1 (d, 2C, *meta*), 35.5, 34.8 (s, each 1C, CMe_3), 30.5, 30.2, 30.1, 28.0 (q, each 3C, *t*Bu), 22.4, 18.5 (s, each 1C, CMe_3, −30°C); ^{11}B-NMR: $\delta = 47$ (1B, BC_3), 9 (1B, B–N); MS (*m/z*, 28 eV): 252 ($M^+ - 135$, 1.4%), 135 ($M^+ - 252$, 100).—**2a**: ^{13}C-NMR (DMSO): $\delta = 181.6$ (s, ring C atoms), 34.5 (s, CMe_3), 27.3 (q, *t*Bu).

[8] H. Klusik, A. Berndt, *Angew. Chem. 95* (1983) 895; *Angew. Chem. Int. Ed. Engl. 22* (1983) 877.

[9] Replacement of a Me_3C group by a Me_3Sn group in di-*tert* butylacetylene leads to a comparable downfield shift: B. Wrackmeyer, *J. Organomet. Chem. 166* (1979) 353.

[10] Note added in proof (December 19, 1983): In the meantime the following values have been measured for the chemical shifts of the ring atoms of **1e**: $\delta(^{13}C) = 180.1$, $\delta(^{11}B) = 35.9$ or 38.5. P. H. M. Budzelaar, P. von R. Schleyer, private communication.

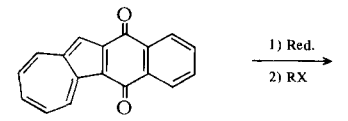
[11] We consider the comparison of **1d** with **4** instead of with an unknown 1-bis(trimethylsilyl)aminoborirane as justified, since trialkylboranes and alkylboriranes exhibit similar $\delta(^{11}B)$-values.

[12] W. Biffar, H. Nöth, H. Pommerening, R. Schwerthöffer, W. Storch, B. Wrackmeyer, *Chem. Ber. 114* (1981) 49.

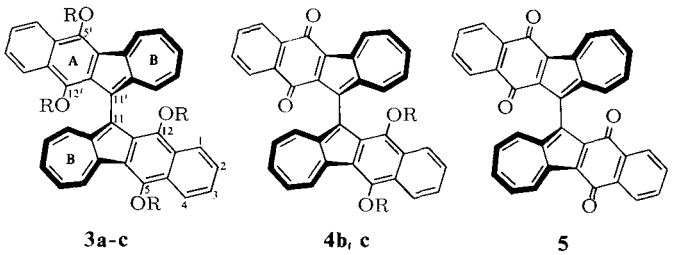
Chiral Electron Transfer Compounds: Binaphtho[2,3-*a*]azulenequinone and Binaphtho[2,3-*a*]azulenehydroquinone Derivatives by Oxidative Coupling**

By *Johann Bindl, Georgios Pilidis,* and *Jörg Daub**

Acenazulenediones, like the naphthoazulenequinone **1**, associate on electrochemical reduction in an aprotic medium[1]. The association of light-sensitive compounds plays an important role in electron transfer processes in chemical and biological systems; *poly*functional chiral compounds containing the structural unit **1** are therefore of



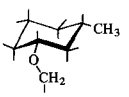
1 **2a–c**



3a–c **4b, c** **5**

a, R = CH_3

b, R = CH_2OCH_3

c, R = 

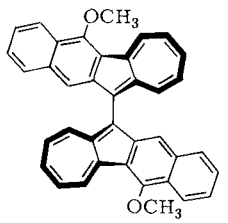


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Table 1. Product composition in the oxidation of **2a–c**. The compounds **1**, **3**, **4**, and **5** were separated chromatographically [5].

Starting cpd., Reaction conditions	Conversion [%]	Yields [%] [a] 1	3	4	5
2a, $FeCl_3$ in DMF [b], 20 h, RT	90	—	90	—	—
2b, PCC [b] in CH_2Cl_2, 40 min, 0°C	100	9	34	30	traces
2c, PCC [b] in CH_2Cl_2, 4 h, RT	55	32	traces	14	traces

[a] Referred to unreacted starting compound. [b] DMF = dimethylformamide, PCC = pyridinium chlorochromate.

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great interest. The racemate of an acenazulenedione has already been described[2]. We now report on the synthesis and stereochemical properties of binaphthoazulenequinones and the corresponding hydroquinone derivatives[3].

Reduction of **1** with sodium dithionite in an alkaline medium and subsequent alkylation with dimethyl sulfate, methoxymethyl chloride, or (−)-3-menthyloxymethyl chloride[4], furnishes the substituted azulenes **2a**, **2b** and **2c**, respectively, in good yields[5]. The oxidative coupling of **2a** leads exclusively to the tetramethoxy compound **3a**, whereas the oxidations of **2b** and **2c** afford product mixtures (Table 1).

4c exists as a diastereomeric mixture of the composition 65:35 ($de = 30\%$) (determined by integration of the OCH_2-absorptions in the ^{1}H-NMR spectrum). In all cases the coupling in the oxidation of compounds **2** takes place only at C-11[6]. The formation of product mixtures in the oxidation of **2b** and **2c** signals the ready oxidative cleavage of the acetal protecting groups, whereby dimerization is obviously difficult in the case of the larger menthyl moiety.

The acid-catalyzed cleavage of the methoxymethyl groups in **3** (tetrahydrofuran, isopropyl alcohol, HCl) and subsequent oxidation with atmospheric oxygen also leads initially to formation of the dione **4b**. With longer reaction times, only the extremely sensitive bisdione **5**[5] is formed.

The ^{1}H-NMR spectra of **3a** and **3b** recorded at different temperatures evidence marked intramolecular interactions in these compounds: In the 250-MHz ^{1}H-NMR spectrum of **3a** at −70°C all the signals are extensively broadened; at +30°C the signals of the ring protons are still extensively broadened. Normal line widths are first observed in spectra recorded above +60°C (Fig. 1). A comparable

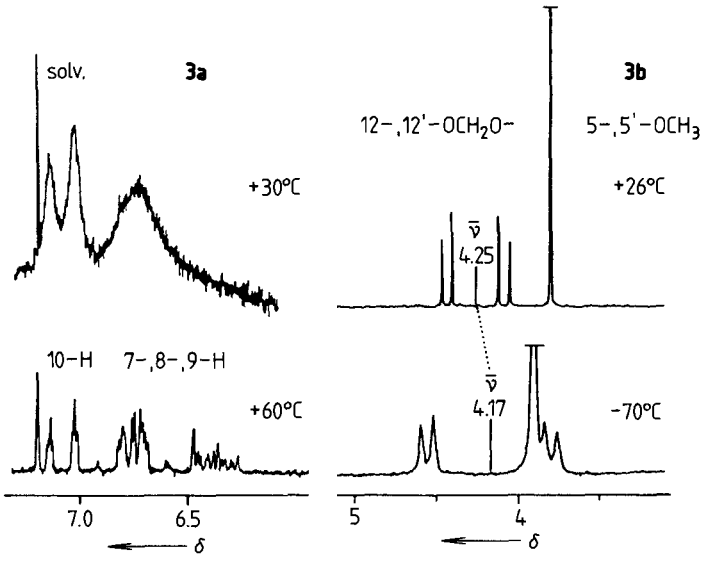
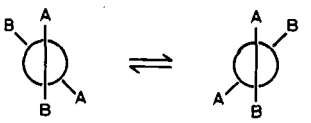


Fig. 1. Parts of the 250-MHz ^{1}H-NMR spectra (in $CDCl_3$) of **3a** and **3b** at various temperatures. **3b**: $\nu_A = 4.08$, $\nu_B = 4.42$, $J_{AB} = 5.7$ Hz.

line-broadening is not observable in the ^{1}H-NMR spectrum of the 5,5'-bismethoxy compound recorded at −80°C[7]. In the case of **3b** the protons of two of the four methylene groups give an AB spectrum up to the highest measuring temperature of 152°C (Fig. 1). We ascribe these bands to the "inner" methoxymethyl groups bound to C-12 and C-12'. The same is observed in the case of **4b**. Moreover, the chemical shifts ν_A and ν_B of **3b** are temperature-dependent.



Scheme 1. Atropisomerism of the chiral binaphthoazulenes. Definition for A, B see **3**.

The spectral data of **3a** and **3b** provide proof of the high "racemization threshold", from which stable enantiomers can be expected[8]; however, because of the sparing solubility, a resolution of the enantiomers has not yet been realized. The DNMR spectra of **3a** and **6** indicate an additional restriction to rotation about the C(12)–O and C(12')–O bonding. The "twisted" arrangement of the two halves of the azulenequinone in **5** (see Scheme 1) can be deduced from the electronic spectra: Aside from a weak bathochromic shift of the two long-wave absorption bands in **5** in comparison to **1**, almost a doubling of the extinction coefficients is found over the whole range of measurement (Fig. 2).

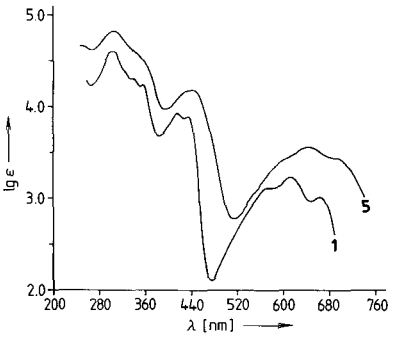


Fig. 2. Electronic spectra of **1** and **5**.

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CAS Registry numbers:
1, 76319-75-0; **2** (R=H), 89398-66-3; **2a**, 89398-67-4; **2b**, 89398-68-5; **2c**, 89398-69-6; (+)-**3a**, 89398-70-9; (+)-**3b**, 89398-71-0; **3c**, 89398-72-1; (+)-**4b**, 89398-73-2; **4c** isomer 1, 89398-74-3; **4c** isomer 2, 89460-89-9; (+)-**5**, 89398-75-4; (+)-**6**, 89398-76-5; dimethyl sulfate, 77-78-1; methoxymethyl chloride, 107-30-2; (−)-methyloxymethyl chloride, 26127-08-2

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[2] J. Bindl, J. Daub, A. Hasenhündl, M. Meinert, K. M. Rapp, *Chem. Ber. 116* (1983) 2408.
[3] J. Bindl, J. Daub, delivered in part in a lecture at the 29th IUPAC Congress, Köln 1983, Program p. 55.
[4] K. A. Andrianov, A. A. Mamedov, L. M. Volkova, E. I. Klabunovskii, *Izv. Akad. Nauk SSSR, Ser. Khim. 1969*, 2305; *Chem. Abstr. 72* (1970) 43888z.
[5] **2a**: Black needles, m.p. 148–149°C; IR (KBr): 1610, 1570 cm^{-1}; ^{1}H-NMR (60 MHz, $CDCl_3$): $\delta = 4.02$ (s, 3H, OCH_3), 4.08 (s, 3H, OCH_3), 6.17–6.87 (m, 3H, H-7,8,9), 7.18 (s, 1H, H-11), 7.26–7.67 (m, 3H), 8.26–8.42 (m, 3H). **2b**: Blue-green oil; IR (film): 1610, 1600, 1575 cm^{-1}.—**2c**: Blue-green solid; m.p. 57–59°C; IR (film): 1610, 1565 cm^{-1}. **3a**: Black crystals; m.p. 297–298°C; IR (KBr): 1610, 1590, 1570 cm^{-1}; ^{1}H-NMR (90 MHz, $CDCl_3$, 60°C): $\delta = 3.26$ (s, 6H, 12-OCH_3, 12'-OCH_3), 4.22 (s, 6H, 5-OCH_3, 5'-OCH_3).—**3b**: Black crystals; m.p. 187.5–188.5°C; IR (KBr): 1610, 1595, 1575 cm^{-1}.—**4b**: Black needles; m.p. 254–256°C; IR (KBr): 1655, 1630, 1585, 1570 cm^{-1}.—**4b**: Moss-green solid; m.p. 70–72°C; IR (KBr): 1660, 1630, 1590, 1570 cm^{-1}.—**5**: Green-brown crystals; m.p. >300°C; IR (KBr): 1660, 1635, 1590, 1575 cm^{-1}.

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[6] Syntheses of biazulenes coupled via the five-membered rings: R. Hagen, E. Heilbronner, P. A. Straub, *Helv. Chim. Acta 51* (1968) 45; M. Pailer, H. Lobenwein, *Monatsh. Chem. 102* (1971) 1558; T. Morita, K. Takase, *Bull. Chem. Soc. Jpn. 55* (1982) 1144.

[7] **6** [black crystals, m.p. 259–261 °C; IR (KBr): 1610, 1595, 1570 cm^{-1}; ^1H-NMR (250 MHz, CH_2Cl_2): $\delta = 4.27$ (s, 6H, 5-OCH_3, 5'-OCH_3), 7.69 (s, 2H, H-12, 12')] was synthesized from **1** by reduction with HI/HOAc, alkylation with Me_2SO_4/NaOH, and subsequent oxidative coupling ($FeCl_3$/DMF).

[8] Cf. also A. Tajiri, M. Fukuda, M. Hatano, T. Morita, K. Takase, *Angew. Chem. 95* (1983) 911; *Angew. Chem. Int. Ed. Engl. 22* (1983) 870; *Angew. Chem. Suppl. 1983*, 1283.

Electrochemiluminescence of Tetrakis(diphosphonato)diplatinate(II)**

By *Arnd Vogler** and *Horst Kunkely*

Intermolecular photoredox reactions of electronically excited transition metal complexes with reducing or oxidizing agents have been the subject of intensive study in recent years[1]. The converse of such processes leads, under suitable conditions, to chemiluminescence (CL). A special case is electrochemiluminescence (ECL). So far only a few investigations have been carried out on the CL[2] or ECL[3] of metal complexes, even though such studies provide important information on the mechanism of redox reactions; hitherto, such investigations have been restricted to complexes which contain 2,2'-bipyridyl or related ligands. The luminescent states are almost exclusively of the charge transfer (metal→ligand)-type. Herein we report on the ECL of $[Pt_2(P_2H_2O_5)_4]^{4\ominus}$ ($A^{4\ominus}$). Both the associated redox processes as well as the ECL itself lead to changes in the metal-metal bonding in the binuclear platinum complex.

In $A^{4\ominus}$ the two Pt^{II} centers are bridged by the dianions of the diphosphonic acid. The metal-metal interaction gives rise to the following series of MOs in order of increasing energy: $1a_{1g}(5d_{z^2}) < 1a_{2u}(5d_{z^2}) < 2a_{1g}(6p_z) < 2a_{2u}(6p_z)$[4]. The a_{1g} orbitals are bonding and the a_{2u} orbitals are antibonding. In the ground state of $A^{4\ominus}$ ($1a_{1g}^2 1a_{2u}^2$) the formal Pt–Pt bond order is therefore 0. At room temperature and in solution, $A^{4\ominus}$ shows an intense photoluminescence of the lowest excited state ($1a_{1g}^2 1a_{2u}^1 2a_{1g}^1$) with bond order 1[4]. Both a weak fluorescence ($\lambda_{max} = 407$ nm) of the singlet $^1A_{2u}$ as well as an intense phosphorescence ($\lambda_{max} = 517$ nm) of the accompanying triplet $^3A_{2u}$ is observed[4].

A 1-cm spectrophotometer cell fitted with two platinum-foil electrodes was used for the ECL investigations. Solutions of $A^{4\ominus}$ as the tetrabutylammonium salt in oxygen-free anhydrous acetonitrile was subjected to an alternating current electrolysis with variable frequency (*sine-wave* generator, Kröncke Mod. 1246) using $nBu_4N^{\oplus}BF_4^{\ominus}$ as supporting electrolyte. With an effective voltage of 4 V and frequency of 280 Hz and a current of 13 mA, a marked green luminescence was observed at one electrode, even with the naked eye. The electrochemiluminescence (Fig. 1) in the long wave region was identical with the photophosphorescence, but no short-wave fluorescence could be observed.

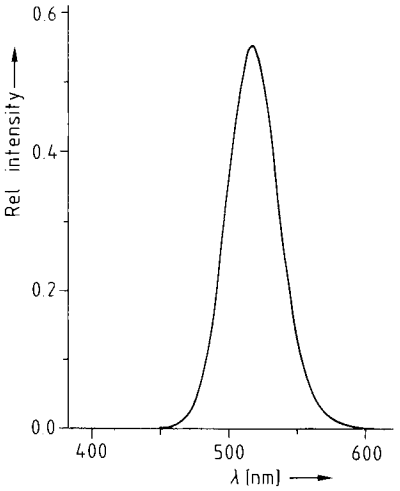

Fig. 1. Electrochemiluminescence spectrum of a solution of 2×10^{-4} M (nBu_4N)$_4$[$Pt(P_2H_2O_5)_4$] and 0.1 M (nBu_4N)BF_4 in CH_3CN; alternating current of 4 V and 280 Hz.

From these observations we conclude that $A^{4\ominus}$ is oxidized to $A^{3\ominus}$ during the anodic phase and reduced to $A^{5\ominus}$ during the cathodic phase. The recombination

$$A^{3\ominus} + A^{5\ominus} \longrightarrow A^{4\ominus *} + A^{4\ominus}$$

furnishes sufficient energy to generate one of the two product molecules in the lowest excited state, the triplet $^3A_{2u}(*)$.

The Pt–Pt bond is strengthened (bond order 1/2), both in the oxidation of $A^{4\ominus}$ to $A^{3\ominus}$ (ground state: $1a_{1g}^2 1a_{2u}^1$) and the reduction to $A^{5\ominus}$ (ground state: $1a_{1g}^2 1a_{2u}^2 2a_{1g}^1$). On the other hand, the recombination involves both a bond-weakening ($A^{4\ominus}$ in the ground state) and bond-strengthening ($A^{4\ominus}$ in the excited state).

Since the ECL spectrum shows only the phosphorescence, and not the fluorescence, the potential difference between $A^{3\ominus}$ and $A^{5\ominus}$ is only sufficient to reach the lowest triplet $^3A_{2u}$ (≈ 2.6 V). The energy of the superposing singlet $^1A_{2u}$ (≈ 3.3 V) is apparently not attained anymore.

The high frequency necessary for observation of the ECL would indicate that the oxidized ($A^{3\ominus}$) or reduced complex ($A^{5\ominus}$), or both, have a very short half-life. This has recently been confirmed: $A^{3\ominus}$ exists only in the solid state in the form of Pt_2 chains which are bridged by halide $X^{\ominus}$[5]; in solution $A^{3\ominus}$ immediately disproportionates into $A^{4\ominus}$ and $AX_2^{4\ominus}$. $A^{5\ominus}$ was generated by pulse radiolysis, but rapidly disappeared ($k = 2.9 \times 10^4$ s^{-1})[6]. It is therefore understandable that it was not possible to determine the redox potentials for the reversible one-electron process by cyclovoltammetry. On attempting to quench the photoluminescence of $A^{4\ominus}$ by electron donors and acceptors, it was however possible to estimate the redox potentials. Donors such as *N,N*-dimethylaniline ($E_{1/2} = 0.78$ V vs SCE) and *N,N*-dimethyl-*p*-toluidine ($E_{1/2} = 0.65$ V) could not quench the photoemission of $A^{4\ominus}$. Even the strong reducing agent *N,N,N',N'*-tetramethyl-*p*-phenylenediamine ($E_{1/2} = +0.24$ V vs SCE) did not effect reduction of $A^{4\ominus}$ in the $^3A_{2u}$ state. It follows, therefore, that the reduction of $A^{4\ominus}$ in the ground state requires at least $E_{1/2} = -2.3$ V vs SCE. In contrast, the phosphorescence of $A^{4\ominus}$ is quenched by relatively weak acceptors[7]. It is estimated that the oxidation of $A^{4\ominus}$ takes place at potentials of less than $E^0 = +1.6$ V vs NHE. The alternating potential of 4 V (2 V

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cathodic and 2 V anodic) necessary for observation of the ECL is needed for the reduction of $A^{4\ominus}$, whereas smaller potentials should suffice for the oxidation.

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CAS Registry number:
$(n\mathrm{Bu_4N})_4[Pt_2(P_2O_5H_2)_4]$, 89462-52-2

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Na_3P_{21} and Li_3P_{21}, the First Polyphosphides with Isolated P_{21}^{3-} Groups**

By *Marianne Baudler*, Doris Düster, Klaus Langerbeins,* and *Joachim Germeshausen*

We recently reported on the synthesis of the polyphosphides Li_3P_7[1] and Li_2P_{16}[2] by nucleophilic cleavage of white phosphorus with lithium dihydrogen phosphide. Salts containing isolated P_n^{m-} anions are of current interest because of their structural relationship with the phosphorus hydrides P_nH_m and organophosphanes P_nR_m and because of their potential use as building blocks for the synthesis of novel polyphosphorus compounds. Herein we report on the synthesis of a trisodium henicosaphosphide and a trilithium henicosaphosphide containing isolated P_{21}^{3-} groups.

Na_3P_{21} **1**[3] is formed on reaction of white phosphorus with substoichiometric amounts of sodium in 1,2-dimethoxyethane or tetrahydrofuran (THF). Other products of the reaction include Na_2P_{16}[4], Na_2HP_7[4], and further, as yet unidentified polyphosphides. The product pattern is strongly dependent on the reaction conditions: The best crude yield of **1** (up to 75 P-% of the soluble reaction products) is obtained at a P : Na ratio of 2 : 1 (not 7 : 1!) in boiling THF. $Na_3P_{21}\cdot 15\,THF$, a solvent adduct of **1**, can be isolated analytically pure by crystallization at −20 °C. On drying, the orange needle-shaped crystals lose a part of the solvent of crystallization with concomitant decomposition to Na_2P_{16} and other polyphosphides. Above −10 °C liquefaction occurs, whereas at room temperature slow disproportionation takes place. The henicosaphosphide is only slightly sensitive to oxidation but strongly sensitive to hydrolysis.

Li_3P_{21} **2** is formed as main product on reaction of Li_3P_7[1,5] with iodine or 1,2-dibromoethane as well as on metalation of P_7H_3[5] with lithium dihydrogen phosphide or *n*-butyllithium under suitable reaction conditions[6]. **2** is also formed on decomposition of LiH_2P_7[7] and Li_2HP_7[7] at room temperature and on nucleophilic cleavage of white phosphorus[8]. Because of the similarity to **1** we have not isolated **2**.

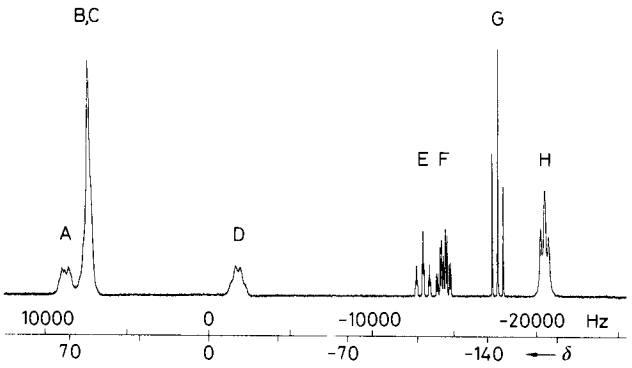
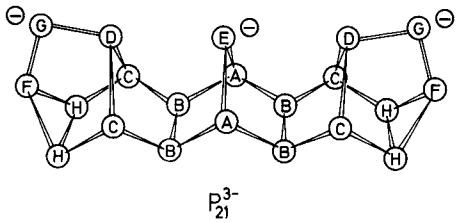


Fig. 1. ^{31}P-NMR spectrum of Na_3P_{21} in tetrahydrofuran/dimethylformamide (ca. 2 : 1) at 243 K (121.497 MHz).

1 and **2** show identical ^{31}P-NMR spectra, in which seven groups of signals occur at $\delta = +72$, $+61$, -15, -108, -118, -146 and -169 (intensity ratio 2 : 8 : 2 : 1 : 2 : 2 : 4) (Fig. 1). The number and intensities of the groups indicate a symmetrical P_{21} skeleton. On the basis of their splitting patterns, chemical shifts and relative



P_{21}^{3-}

intensities the signal groups D, F, G, and H are each to be assigned to five P atoms from two equivalent P_7 cages with nortricyclene structure[9]. As evidenced by the triplet-like signal group E, a P_7-substructure analogous to norbornane with negative charge on the P atom of the P_1-bridge is present as linkage between the two cages. Correspondingly, from the intensities of the remaining signals it follows that the downfield group A arises from the two central bridgehead atoms[10], while the neighboring intense signal B, C arises from the remaining two pairs of four equivalent P atoms.

The constitution of the P_{21}^{3-} ion as decacyclo-[9.9.1.$0^{2,10}$.$0^{3,7}$.$0^{4,9}$.$0^{6,8}$.$0^{12,20}$.$0^{13,17}$.$0^{14,19}$.$0^{16,18}$]henicosaphosphide(3−) is confirmed by the homoscalar-correlated 2D-^{31}P-NMR spectrum (COSY spectrum[11]) of **1** (Fig. 2). All $^1J(PP)$ couplings of the directly linked and non-degenerated P atoms appear as cross-peaks.

The P_{21}^{3-} ion is the largest isolated $P_n(m)$ unit group known so far. In K_4IP_{21} synthesized by *von Schnering* et al.[12] these P_{21}^{3-} groups are linked, after opening of their three-membered rings, to give a polymeric $^2_\infty[P^-_7]$-structure. As a conjuncto-phosphane the isolated $P_{21}(3)$ skeleton is made up of a $P_7(5)$ unit analogous to

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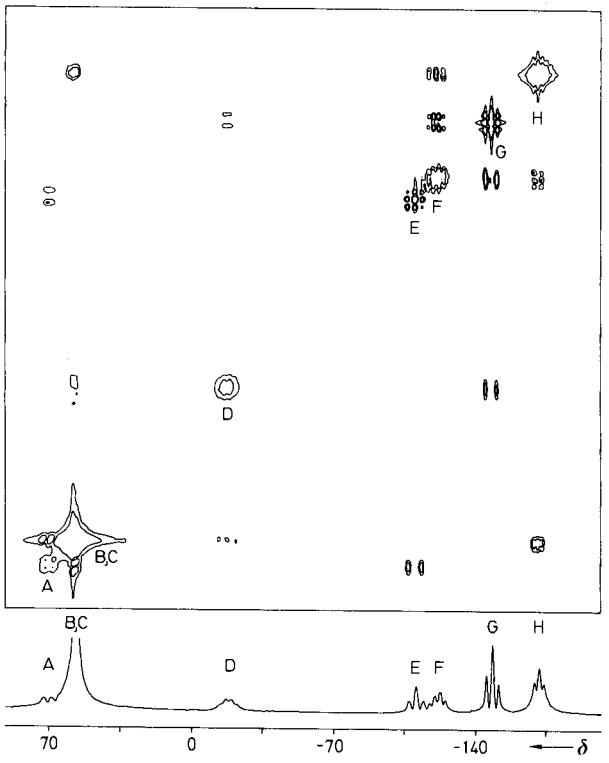

Fig. 2. (Top): Homoscalar-correlated 2D-^{31}P-NMR spectrum (COSY-90) of Na_3P_{21} in tetrahydrofuran/dimethylformamide/[D_7]dimethylformamide at 243 K, multiplication of the FIDs with Gauss function (LB = −100, GB = 0.05) in both dimensions, 512 × 2048 matrix, 1024 × 2048 transformation, measuring frequency 121.497 MHz, measuring time ca. 42 h. (Bottom): Projection onto the F_2 axis.

norbornane and two P_9(3) structural elements, analogous to deltacyclane, which are linked via the diatomic bridges as common zero-bridges to two P_8(6) substructures analogous to pentalane. The corresponding polycycloalkane $C_{21}H_{24}$ has been known for some time[13].

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CAS Registry numbers:
1, 89462-41-9; **2**, 89462-42-0; P, 7723-14-0; Na, 7440-23-5; Li, 7439-93-2; Li_3P_7, 72976-70-6; P_7H_3, 51273-53-1; LiH_2P_7, 89462-43-1; Li_2HP_7, 89462-44-2; LiH_2P, 24167-79-1; *n*-BuLi, 109-72-8

[1] M. Baudler, W. Faber, *Chem. Ber. 113* (1980) 3394.
[2] M. Baudler, O. Exner, *Chem. Ber. 116* (1983) 1268.
[3] Procedure for **1**: Freshly distilled white phosphorus (3.0 g, 0.097 g-atom) and powdered sodium (1.1 g, 0.048 g-atom) in THF (150 mL) are slowly stirred and heated under reflux for 2.5 h under inert gas. The solution turns red, and a fine black precipitate separates out. After removal of the solid by filtration (reduced pressure) at room temperature the filtrate is cooled to −20°C and allowed to stand until completion of crystallization. The crude product is filtered off in the cold (without reduced pressure!) and washed five times with 10 mL of cold THF. Dissolution in 20 mL THF at 0°C and renewed crystallization at −20°C yields pure **1**, which is filtered cold and dried under oil pump vacuum for 15 s; yield 3.0 g $Na_3P_{21}\cdot 15$ THF (36%). Further amounts of **1** can be recovered from the mother liquor.
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Stereoselective Total Synthesis of Chlamydocin and Dihydrochlamydocin**

By *Ulrich Schmidt**, *Albrecht Lieberknecht*, *Helmut Griesser*, and *Frank Bartkowiak*

Chlamydocin **8**[1], a cyclic tetrapeptide with extremely high cytostatic activity in vitro, was isolated together with dihydrochlamydocin **7** from culture filtrates of *Diheterospora chlamydosporia*, and its structure and conformation was elucidated in 1976[1,2]. We recently reported[3] on a synthesis of chlamydocin + *epi*-chlamydocin, for epoxidation of the corresponding vinyl ketone proceeded without asymmetric induction by the peptide ring[***]. We now describe the stereoselective total synthesis of **7** and **8** (Scheme 1), in which the *S,S*-configuration at C^8 and C^9 of the substituted aminodecanoic acid is achieved with the aid of (*R,R*)-tartaric acid and the *S*-configuration at C^2 is formed by enantioselective hydrogenation.

Incorporation of the C^7–C^{10} segment of the (2*S*,8*S*,9*S*)-2-amino-8-hydroxy-9,10-epoxydecanoic acid in **7** can be accomplished with the aldehyde **1**, which is readily accessible from (*R,R*)-tartaric acid[4]. Condensation with triphenyl(4-trimethylsiloxybutylidene)phosphorane[7] and subsequent oxidation led to the C_8-aldehyde **2** (*E/Z* mixture), which was condensed with methyl *N*-benzyloxycarbonyl-2-(dimethoxyphosphinyl)glycinate[8] to give the dehydroamino acid ester **3** (diastereomeric mixture). Enantioselective homogeneous hydrogenation of the *E/Z* mixture with the Monsanto catalyst $[Rh(cod)(dipamp)]^{\oplus}BF_4^{\ominus}$[9] led with high enantioselectivity (*ee* > 98%) to the (*S*)-amino acid derivative. Subsequent heterogeneous hydrogenation of the C^6–C^7 double bond, hydrogenolysis of the benzyl ether and benzyloxycarbonyl protecting group, followed by reincorporation of the protecting group, replacement of OH by Cl, and hydrolysis furnished the amino acid **4**, from which the tetrapeptide pentafluorophenyl ester **5** was synthesized by conventional methods. Ring closure by the method previously developed by us[10] afforded the cyclopeptide **6** in high yield. Absolutely no racemization at the proline was observed, for this would have led to a cyclo-

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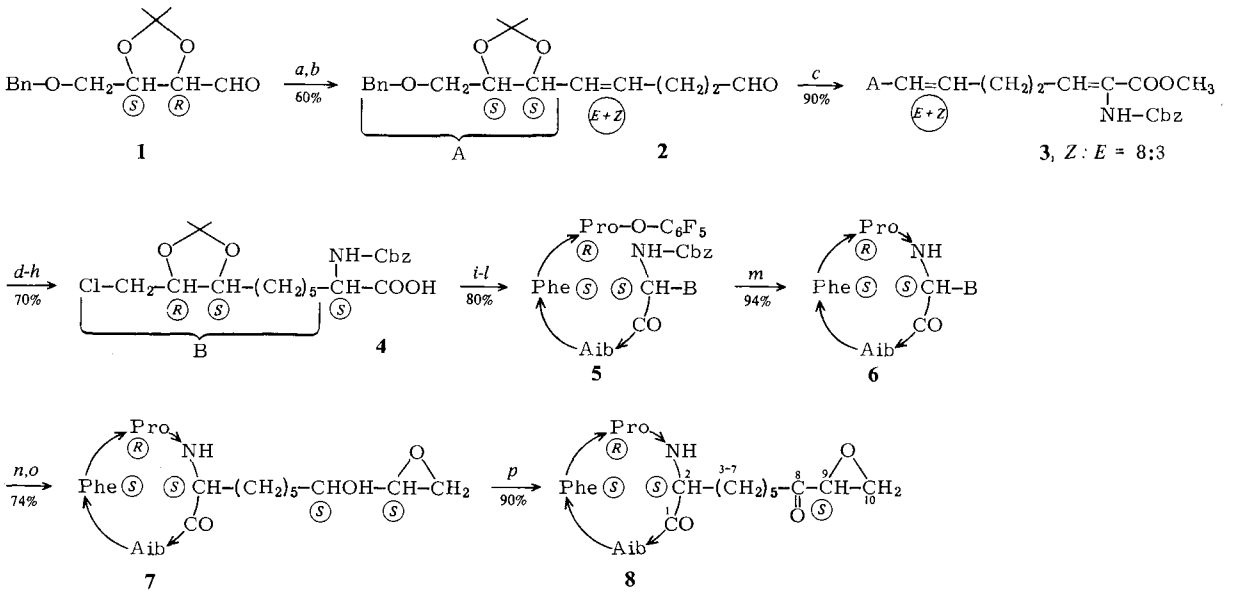
[***] Note added in proof: After submission of the manuscript, a further non-stereoselective synthesis of chlamydocin + 9-*epi*-chlamydocin came to our notice: D. H. Rich, J. Gardner, *Tetrahedron Lett. 24* (1983) 5305.



Scheme 1. Synthesis of chlamydocin **8**. *a:* $Ph_3P^{\oplus}-(CH_2)_4-O-SiMe_3Br^{\ominus}$ + $(Me_3Si)_2NLi$, −70°C, 30 min→RT, 10 h. *b:* Pyridinium chlorochromate, CH_2Cl_2, RT, 1 h. *c:* Methyl *N*-benzyloxycarbonyl-2-(dimethoxyphosphinyl)glycinate, KO-*t*Bu, CH_2Cl_2, −70°C, 30 min. *d:* [Rh(cod)(dipamp)]$^{\oplus}BF_4^{\ominus}/H_2$, EtOH, RT, 3 d, 3 bar [9]. *e:* Pd/H_2, MeOH, RT, 1 d, 3 bar. *f:* Benzyloxycarbonyl chloride. *g:* 1-Chloro-1-dimethylamino-2-methyl-1-propene + pyridine, CH_2Cl_2, −20°C, 30 min, 40°C, 30 min. *h:* $NaOH/H_2O$/dioxane, RT, NaOH added dropwise over 5 h: pH < 11. *i:* H-Aib-(*S*)-Phe-(*R*)-Pro-OCH_3/DCCD, ethyl acetate, −20°C→RT. *k:* $NaOH/H_2O$/dioxane, RT, 5 h. *l:* C_6F_5OH/DCCD/ethyl acetate, −20°C→RT. *m:* H_2/Pd, dioxane, 95°C, 5 h, reaction at high dilution. *n:* Oxalic acid/dioxane/H_2O, 80°C, 4 h. *o:* K_2CO_3/CH_3OH, RT, 4 h. *p:* DCCD/DMSO/dichloroacetic acid. – Bn: benzyl; Cbz: benzyloxycarbonyl.

tetrapeptide with three (*S*)-amino acids. In this series, such isomers are formed in only extremely small yields and are easy to recognize on chromatographic separation.—Hydrolysis of the ketal and epoxidation yielded dihydrochlamydocin **7**, which was oxidized to the chlamydocin **8** with dicyclohexylcarbodiimide (DCCD)/dimethyl sulfoxide (DMSO)/dichloroacetic acid. The NMR spectra and α_D^{20}-values of the synthetic product were identical with those of the natural product. The agreement in the CD spectra is illustrated in Figure 1.

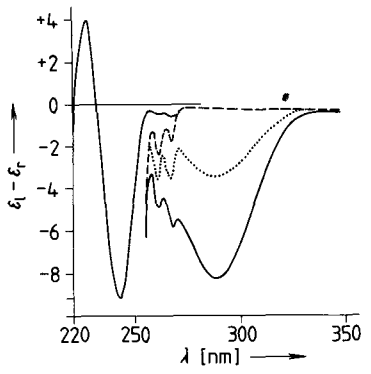
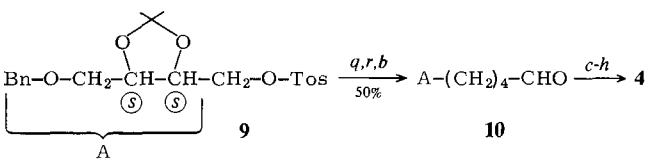


Fig. 1. CD spectra of chlamydocin **8** and epimeric mixtures in ethanol ($c = 3.9 \times 10^{-4}$ mol/L). Absorptions appear in different regions for the peptide ring (220–275 nm) and the epoxyketone group (250–340 nm). (-----): 50% **8** + 50% 9-*epi*-chlamydocin (complete racemization at C^9) [3]; (·····): 70% **8** + 30% 9-*epi*-chlamydocin, obtained by oxidation of **7** with pyridinium chlorochromate; (——): natural chlamydocin **8** and product obtained by oxidation of **7** with DCCD/DMSO/dichloroacetic acid. The curves for $\lambda = 250$–350 nm are tenfold higher than those for $\lambda = 220$–270 nm. 250–350 nm: 2.

An alternative route to the (*S*)-amino acid **4** involved the use of the tartaric acid derivative **9**[5] and the readily accessible 4-trimethylsiloxybutyl cuprate[11] as starting materials. The coupling product was oxidized to the aldehyde **10**, which reacted analogously to **2** to give **4** (Scheme 2).



Scheme 2. Alternative route for the synthesis of the aldehyde **4**. *q:* $[Me_3Si-O-(CH_2)_4]_2LiCu$, diethyl ether, −70°C→RT. *r:* *n*-$Bu_4N^{\oplus}F^{\ominus}$, acetone, RT, 10 min.—For abbreviations see Scheme 1.

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1, 81028-12-8; (*E*)-**2**, 89278-30-8; (*Z*)-**2**, 89361-29-5; **3**, 89278-31-9; **4**, 89278-32-0; **5**, 89321-01-7; **6**, 89278-33-1; **7**, 52574-64-8; **8**, 53342-16-8; **9**, 78513-04-9; **10**, 89278-34-2; $Ph_3P^+-(CH_2)_4-O-SiMe_3Br^-$, 89278-35-3; H-Aib-(*S*)-Phe-(*R*)-Pro-OCH_3, 88568-96-1; *N*-benzyloxycarbonyl-2-(dimethoxyphosphinyl)glycine methyl ester, 88568-95-0; benzyloxycarbonyl chloride, 501-53-1

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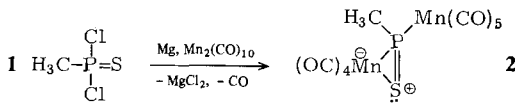
Methyl(thioxo)phosphane: Generation and Trapping Reaction with $Mn_2(CO)_{10}$**

By *Ekkehard Lindner*, Konrad Auch, Wolfgang Hiller,* and *Riad Fawzi*

The generation of diphosphenes by using extremely bulky or electron-rich organic substituents as protecting groups has been reported on a number of occasions just recently[1]. However, to our knowledge, not a single representative of the thioxophosphanes RP=S, which are isoelectronic with diphosphenes RP=PR, has so far been isolated. Owing to its alkene-[2] or alkyne-like[3] behavior, the −P=S function is a valuable building block for the synthesis of numerous heterocycles. We have now been able to trap the intermediate formed on reaction of magnesium[4] with dichloro(methyl)thioxophosphorane **1** in presence of $Mn_2(CO)_{10}$, namely a methyl(thioxo)phosphane[5], whose molecular skeleton remains intact in the complex **2**.



The observation that only traces of the binuclear complex **2** can be detected in the reaction of **1** with $[Mn(CO)_5]^{\ominus}$ points to dehalogenation of **1** by magnesium and thus to an attack of $CH_3P{=}S$ on intact $Mn_2(CO)_{10}$. Attempts to prepare $[Fe_2(CO)_6(P_2tBu_2)]$[6] by analogous addition of RP=S to an $Fe_2(CO)_6$ fragment were unsuccessful; instead, rupture of the P=S bond led to formation of the trinuclear clusters $(\mu_3\text{-}S)(\mu_3\text{-}RP)Fe_3(CO)_9$[7] (R = CH_3, 4-$CH_3OC_6H_4$, C_6H_5).

The air- and moisture-insensitive yellow crystals of **2** (from toluene/*n*-hexane, m.p. 104°C) are readily soluble in polar solvents, but only sparingly soluble in apolar solvents. The binuclear complex was characterized by complete elemental analysis, and by its IR, ^{1}H- and ^{31}P-NMR and mass spectra[8], and an X-ray structure analysis (Fig. 1). Because of the low symmetry of the molecule, nine C≡O absorptions of different intensity are observed for the $Mn(CO)_4$ and $Mn(CO)_5$ fragments in the 5 μm region of the IR spectrum. The CH_3 stretching and deformation vibrations as well as ν(P–C) of the CH_3PS-ligand can be unequivocally assigned.

The X-ray structure analysis of **2** confirms the presence of the methyl(thioxo)phosphane ligand, which is coupled side-on with a $(OC)_4Mn$ complex fragment and end-on via the P atom with a $(OC)_5Mn$ group. The P=S function, with a bond length of 203 pm, should exhibit pronounced π-bonding. The sterically bulky $(OC)_5Mn$ group leads to a noticeable widening of the Mn–P–Mn angle.

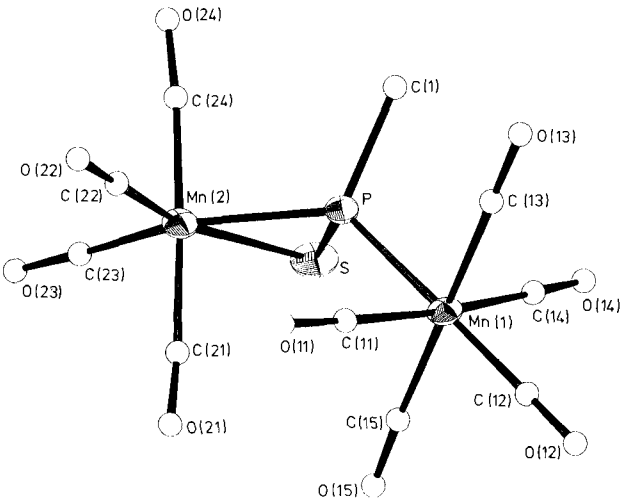


Fig. 1. Molecular structure of **2** in the crystal. Monoclinic, $P2_1/n$, $a = 659.4(3)$, $b = 1520.6(3)$, $c = 1631.2(3)$ pm, $\beta = 93.29(3)°$, $\rho_{calc} = 1.433$ g/cm^3, $Z = 4$, $Mo_{K\alpha}$ radiation. The structure was determined by direct methods (Multan), $R = 0.059$ (1801 symmetry independent reflections with $I \geq 3\sigma(I)$, 4247 measured reflections, 208 refined parameters). Selected bond lengths [pm] and angles [°]: Mn(1)–P 239.4(2), Mn(2)–P 228.9(2), Mn(2)–S 241.4(2), P–S 203.3(2), P–C(1) 184.7(6), Mn(2)–S–P 61.2(1), Mn(2)–P–S 67.6(1), S–Mn(2)–P 51.1(1), Mn(2)–P–Mn(1) 129.4(1), Mn(2)–P–C(1) 117.1(2), Mn(1)–P–S 115.5(1), Mn(1)–P–C(1) 109.3(2), S–P–C(1) 108.7(2). Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2 on quoting the depository number CSD 50677, the names of the authors, and the full citation of the journal.

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[**] Preparation and Properties of and Reactions with Metal-Containing Heterocycles, Part 39. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.—Part 38: E. Lindner, A. Brösamle, *Z. Naturforsch. B*, in press.

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[4] R. D. Rieke, S. E. Bales, *J. Am. Chem. Soc. 96* (1974) 1775.
[5] Procedure: All operations were carried out in anhydrous solvents under an inert gas. A solution of **1** (520 mg, 3.5 mmol) in THF (50 mL) was added dropwise within 3 h at 20°C to a mixture of 240 mg (10 mmol) of highly reactive magnesium (prepared from $MgCl_2$ and potassium in THF [4]) and 980 mg (2.5 mmol) $Mn_2(CO)_{10}$ in 100 mL tetrahydrofuran (THF). After filtration over silica gel (P3) and removal of the solvent in vacuo, column chromatographic separation (silica gel, Act. I, $l = 5$ cm, $\varnothing = 25$ mm, eluent *n*-hexane/CH_2Cl_2 5:1) of the residue dissolved in 10 mL $CHCl_3$ yielded pure **2** as second fraction. Yield 78 mg (7%).
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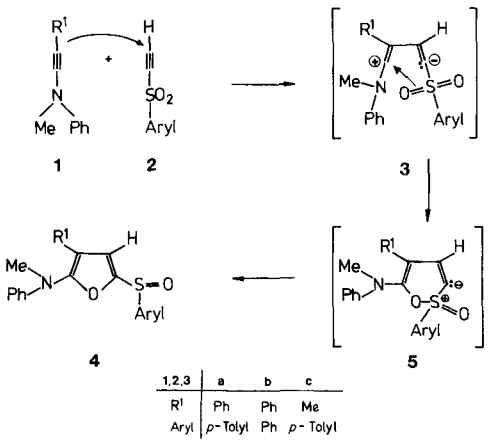
[8] MS (70 eV): *m/z* 440 (M^+), 173 ($PSMn_2^+$).—IR (*n*-hexane): 2124 m, 2071 m, 2064 s, 2038 vs, 2034 vs, 2023 s-vs, 1999 m-s, 1978 s-vs, 1955 s (CO); (KBr): 2970 vw, 2930 vw, 1422 w, 1412 w, 1288 vw, 884 m, 866 w-m (CH_3); 707 cm^{-1} m (PC).—^{1}H-NMR ($CDCl_3$, rel. TMS): $\delta = 2.13$ (d, $^2J_{HP} = 6.4$ Hz, CH_3).—^{31}P[^{1}H]-NMR (CH_2Cl_2, rel. 85% H_3PO_4 ext.): $\delta = 21.6$.

2-Amino-5-sulfinylfurans from Sulfonylacetylenes and Ynamines

By *Gerhard Himbert**, *Steffen Kosack*, and *Gerhard Maas*

Ynamines undergo [2+2]-cycloaddition with electrophilic double bonds to give cyclobutenes which are either stable or spontaneously isomerize[1]. In contrast, reactions of ynamines with acetylenedicarboxylates or nitroacetylenes have been reported not to give cyclobutadienes but benzene derivatives (1:2-addition)[2] and, depending on the structure, also enynamines (aminoethynylmetalation)[3] or nitrile oxides[4]. Also, open-chain 1,4-dipolar species are more likely than cyclobutadienes as intermediates for these products[1]. It was recently reported that *N,N*-diethyl(-1-propynyl)amine should react with phenyl(1-propynyl)sulfone quantitatively to give the corresponding cyclobutadiene[5,6]. We have now found that the reactions of the somewhat less reactive ynamines **1** (these have a methylanilino instead of a diethylamino group) with the sulfonylacetylenes **2** lead smoothly to the 2-amino-5-sulfinylfurans **4**[7].



1,2,3	a	b	c
R^1	Ph	Ph	Me
Aryl	*p*-Tolyl	Ph	*p*-Tolyl

We presume that the reaction is initiated by a nucleophilic attack of the ynamine β-C atom at the terminal C atom of the sulfonylacetylene. The zwitterion **3** thus formed then cyclizes via the S=O bond to give the "ylidic" heterocycle **5**, which finally furnishes the furans **4** in the sense of a Pummerer rearrangement[8].

First indications of the structure of our 1:1 adducts, and thus of the participation of the sulfonyl group in the reaction, were provided by the IR spectra: They are essentially free of bands in the regions characteristic for SO_2 vibrations around 1150 and 1300–1350 cm^{-1}. An intense absorption at about 1045 cm^{-1} (Table 1) points to the presence of a sulfinyl group. Particularly characteristic in the ^{1}H-NMR spectra are the singlet of the proton at position 4 of the furan moiety and the doublet of the corresponding ^{13}C-atom ($^1J_{C,H}=178$ Hz) (Table 1).

Although the furan derivative **4a** can be reduced to the sulfide [yield 10%; m.p. 108–109°C; ^{1}H-NMR ($CDCl_3$): $\delta=7.03$ (s; 1H, furyl-4*H*)] and oxidized to the sulfone [36%; m.p. 137–138°C; ^{1}H-NMR ($CDCl_3$): $\delta=7.46$ (s; 1H, furyl-4*H*); IR (KBr): $\nu=1327$ s, 1161 s, 1141 s cm^{-1} (SO_2 region)], attempted chemical identification by derivatization or hydrolysis has so far met without success. The constitution of **4a** was therefore elucidated by an X-ray structure analysis (Fig. 1)[9].

Table 1. Yields and some physical data of the 2-amino-5-sulfinylfurans **4**.

4	Yield [%] (M.p. [°C]) [a]	IR (KBr) [cm^{-1}] C=C	S=O	^{1}H-NMR ($CDCl_3$; δ values) Characteristic signals [b]
a [d]	52–64 [c] (116–117)	1616 m 1592 s 1578 sh 1509 sh 1488 s	1045 s	2.42 (s; 3H, aryl-*Me*) 3.17 (s; 3H, N*Me*) 7.04 (s; 1H, furyl-4H)
b	67 (114–115)	1611 m 1592 s 1578 sh 1511 sh 1492 s	1048 s	3.16 (s; 3H, N*Me*) 7.09 (s; 1H, furyl-4H)
c	55 (61–62)	1625 m 1595 s 1576 sh 1488 s	1041 s	1.76 (s; 3H, furyl-*Me*) 2.42 (s; 3H, aryl-*Me*) 3.21 (s; 3H, *N*Me) 6.61 (s; 1H, furyl-4H)

[a] Melts with decomposition. [b] The singlet for the furyl proton in position 4 is recognizable with some degree of certainty; in the case of **4a** the assignment is confirmed by the use of deuterated sulfonylacetylene. [c] 87% yield on using a 2.5-fold excess of ynamine. [d] ^{13}C-NMR ($CDCl_3$, 50.28 MHz): $\delta=21.50$ (q; aryl-CH_3), 38.00 (q; N-CH_3), 114.61, 125.06, 126.45, 128.74, 129.06, 130.01 (6d; *o*- and *m*-*C* of the three phenyl rings), 120.18, 127.43, 141.86 (2d+1s; *p*-*C* of the three phenyl rings), 130.70, 138.27, 145.70 (3s; *ipso*-*C* of the three phenyl rings), 116.02 (s; C3), 116.89 (d; $J=178$ Hz; C4), 148.74 (s; C5), 152.51 (s; C2).

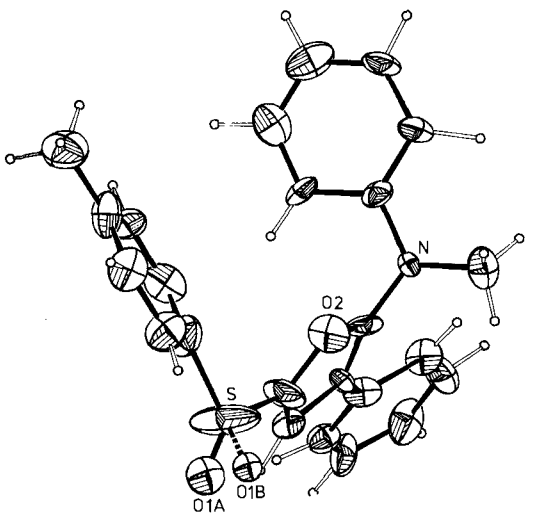


Fig. 1. Structure of an independent molecule of **4a** in the crystal (ORTEP plot). Vibration ellipsoids: 33% probability level. The oxygen atom of the sulfoxide group is disordered (exchange with a lone pair at the sulfur atom). Such a disorder also seems to be present in the second molecule; it could not however be meaningfully refined.

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1 (R^1=Ph), 32907-84-9; **1** (R^1=Me), 4231-29-2; **2** (Aryl=*p*-tolyl), 13894-21-8; **2** (Aryl=Ph), 32501-94-3; **4a**, 89438-33-5; **4a** sulfide, 89438-36-8; **4a** sulfone, 89438-37-9; **4b**, 89438-34-6; **4c**, 89438-35-7

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[6] Although we could confirm most of the ^{1}H-NMR data quoted in [5] we still cannot give a definite statement about the structure of the adduct or the new compound formed from it on distillation.
[7] Part of a Diplomarbeit by *S. K.*; X-ray structure analysis by *G. M.*
[8] The formation of cyclobutadienes as intermediates cannot be ruled out, but, in our opinion, seems highly unlikely for energetic reasons.
[9] **4a**: Orthorhombic, $a=9.446(3)$, $b=19.937(4)$, $c=21.416(7)$ Å, $\alpha=\beta=\gamma=90°$; space group $Pca2_1$, $Z=8$ (two independent molecules), $\rho_{calc}=1.276$ g cm^{-3}. Data collection: Enraf-Nonius CAD4 diffractometer, 2633 independent reflections with $2.00<\theta<22.00°$. Refinement: $R=0.087$, $R_w=0.081$ (2279 reflections with $I>2\sigma(I)$, $w=1/(\sigma^2+(0.023F_0)^2)$, heavy atoms anisotropic, disordered O atoms of the sulfoxide group isotropic, H atoms with $B=7.0$ Å^2 (only in calculation of structure factors). Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD 50698, the names of the authors, and full citation of the journal.

Synthesis and Crystal Structure of the Dicarbido Bimetallic Cluster $[Co_6Ni_2C_2(CO)_{16}]^{2-}$**

By *Aurora Arrigoni, Alessandro Ceriotti, Roberto Della Pergola, Giuliano Longoni*, Mario Manassero*, Norberto Masciocchi,* and *Mirella Sansoni*

Recently, we reported the synthesis and structural characterization of the carbido cluster $[Co_3Ni_9C(CO)_{20}]^{3-}$ **1**[1,2]. We report here the synthesis and crystal structure of a chemically related bimetallic dicarbido cluster, namely the dianion $[Co_6Ni_2C_2(CO)_{16}]^{2-}$ **2**, which is the first simple-hexagonal array of metal atoms whose cavity is completely filled by carbido C atoms.

The dicarbido cluster **2** was originally detected by IR spectroscopy, together with several other species, in the reaction of $[Co_3(CO)_9CCl]$ **3** with $[Ni_6(CO)_{12}]^{2-}$ **4** when **3** and **4** are allowed to react in a molar ratio greater than that used previously to synthesize **1**[1,2]. **2** can be synthesized selectively from **1** and **3** according to equation (a) or by slow addition of **4** to **3** (ca. 1:2 molar ratio) in tetrahydrofuran (THF) [equation (b)]. The dianion **2** has been isolated in more than 70% yield with several tetrasubstituted ammonium or phosphonium counterions; the $Et_4N^{\oplus}$ salt has been crystallized from acetone/heptane[3].

$$2\,[Co_3Ni_9C(CO)_{20}]^{3-} + 4\,[Co_3(CO)_9CCl] \longrightarrow 3\,[Co_6Ni_2C_2(CO)_{16}]^{2-} + 2\,NiCl_2 + 7\,Ni(CO)_4 + 3\,Ni \quad \text{(a)}$$

1 **3** **2**

$$2\,[Co_3(CO)_9CCl] + [Ni_6(CO)_{12}]^{2-} \longrightarrow [Co_6Ni_2C_2(CO)_{16}]^{2-} + NiCl_2 + 3\,Ni(CO)_4 + 2\,CO \quad \text{(b)}$$

3 **4** **2**

The structure of the $Et_4N^{\oplus}$ salt of **2** has been elucidated by X-ray diffraction (Fig. 1)[4]. Dianion **2** has a crystallographic C_i-$\bar{1}$ and an idealized C_{2h}-2/m symmetry and originates from the condensation of two trigonal-prismatic moieties sharing a common square face. An idealized mirror plane is defined by atoms Co1, Co1′, Ni3, and Ni3′. The metal framework of **2** represents a fragment of a simple hexagonal metal lattice, which is stabilized by filling each of the two trigonal prismatic cavities with two carbido C atoms[5]. Previously described clusters having this type of trigonal prismatic building unit are, for instance, $[Rh_6C(CO)_{15}]^{2-}$[6], and the pseudo one-dimensional oligomers $[Pt_3(CO)_6]_n^{2-}$ (n = 2–5)[7].

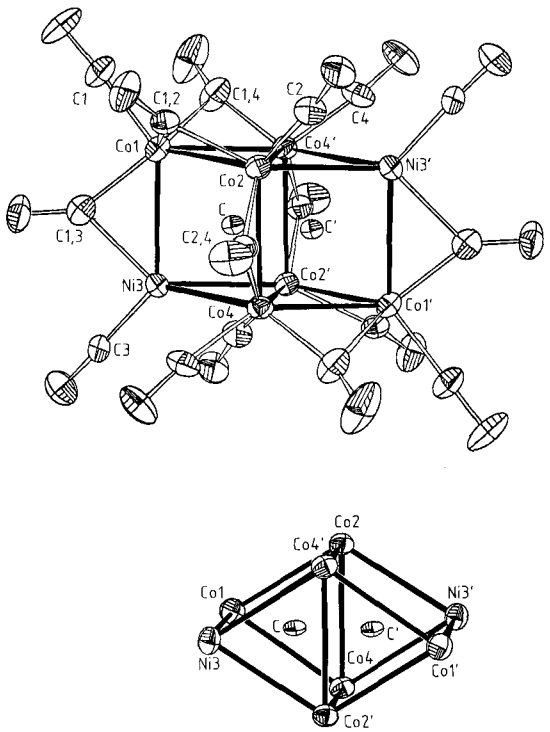

Fig. 1. ORTEP view of the structure of **2** in the crystal. Complete dianion (top) and naked metal framework with the two interstitial C atoms (bottom). Most important distances [Å]: M–M: Co1-Co2 = 2.577(1), Co1-Co4 = 2.528(1), Co1-Ni3 = 2.548(1), Co2-Co4 = 2.775(1), Co2-Co4′ = 2.559(1), Co2-Ni3′ = 2.647(1), Ni3-Co4′ = 2.590(1). – M–$C_{carbido}$: Co1-C = 1.953(5), Co2-C = 2.048(6), Ni3-C = 1.885(5), Co4-C = 2.031(5), Co2′-C = 2.017(6), Co4′-C = 2.023(6). – M–$CO_{terminal}$: Co1-C1 = 1.755(8), Co2-C2 = 1.753(8), Co4-C4 = 1.739(8), Ni3-C3 = 1.774(8). – M–$CO_{bridging}$: Co1-C1,3 = 1.845(8), Co1-C1,2 = 2.317(8), Co1-C1,4 = 2.034(7), Co2-C1,2 = 1.797(8), Co2-C2,4 = 1.956(7), Ni3-C1,3 = 1.967(7), Co4-C1,4 = 1.866(7), Co4-C2,4 = 1.929(7). – C–O: C1-O1 = 1.131(8), C2-O2 = 1.160(8), C3-O3 = 1.117(8), C4-O4 = 1.149(8), C1,3-O1,3 = 1.142(8), C1,2-O1,2 = 1.169(8), C1,4-O1,4 = 1.163(8), C2,4-O2,4 = 1.157(8). – C–C′ = 1.494(11).

In accord with analytical data[3], two atoms of **2** are less coordinated by CO ligands, and we presume that they are Ni atoms. The distance between the two carbido C atoms of 1.49 Å is shorter than typical CC single bonds in hydrocarbons (1.54 Å) and than most C···C interatomic separations in other dicarbido clusters[8,9]. Only the neutral Rh cluster $[Rh_{12}C_2(CO)_{25}]$ and the $[Co_{11}C_2(CO)_{22}]^{3-}$ trianion[10,11], whose metal frameworks originate from condensation of square-antiprismatic and trigonal prismatic moie-

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ties, respectively, show comparably short CC interatomic separations (1.48 and 1.62 Å, respectively); an even shorter distance (1.41 Å) is exhibited by the trianion $[Co_3Ni_7C_2(CO)_{15}]^{3-}$[1]. In both $[Rh_{12}C_2(CO)_{25}]$ and $[Co_{11}C_2(CO)_{22}]^{3-}$, the calculated distances between the centers of the two idealized cavities (with edge length equal to the overall mean value of the M–M bonds) are longer than the experimentally determined CC distances (1.98 and 1.80 Å, respectively)[11]. In contrast, in **2** the corresponding calculated and experimental distances (1.49 Å) almost coincide. Such a short interatomic CC separation would be in keeping with the presence of a localized CC bonding interaction in **2**. However, the number of valence electrons (n_{CVE}) of the known carbonylmetal clusters of the first transition series systematically conforms to the relationship $n_{CVE} \geqslant 18N - 2n_{M-M}$ (where N and n_{M-M} are, respectively, the number of metal atoms and M–M bonds). Furthermore, EHMO calculations on a naked cluster having the idealized metal geometry of the title compound predict 58 cluster valence MOs[12]. **2** would therefore require at least 116 cluster valence electrons, which is fulfilled only if each interstitial C atom contributes four skeletal electrons. In accord with this, the thermal ellipsoids of the two carbido C atoms elongated in the CC direction appear to argue against the presence of a localized C–C bond in **2** and suggest a delocalized CC interaction supported by the metal atoms.

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2·2Et_4N, 89462-35-1; **3**, 13682-02-5; Ni, 7440-02-0; Co, 7440-48-4

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[3] *Procedure:* A solution of $Co_3(CO)_9CCl$ (0.24 g) in 9 mL acetone was added dropwise to a stirred solution of $[NEt_4]_3[Co_3Ni_9C(CO)_{20}]$ (0.42 g) in 20 mL acetone. After 3 h, the reaction solution was evaporated to dryness in vacuo to eliminate $Ni(CO)_4$, and the residue was taken up in acetone (20 mL). Precipitation by slow diffusion of *n*-heptane (30 mL) afforded 0.31 g of the $Et_4N^{\oplus}$ salt of **2** as black crystals. **2** as its $Et_4N^{\oplus}$ salt is diamagnetic and its ^{1}H-NMR spectrum shows no signals other than those of the cation (30 and −75 °C). Carbonyl absorptions occur at 2040 (vw), 2010 (vs), 1987 (sh), 1977 (s), 1931 (ms), 1829 (m), and 1797 (w) cm^{-1} in the IR spectrum (THF). Elemental analysis: Calcd. $Et_4N^{\oplus}$ 21.62, Co 29.38, Ni 9.76, CO 37.26; $Et_4N^{\oplus}$:Co:Ni = 1:3:1. Found: $Et_4N^{\oplus}$ 21.3, Co 29.2, Ni 9.3; $Et_4N^{\oplus}$:Co:Ni = 1:3.03:0.98.
[4] Monoclinic, space group $P2_1/c$; $a = 9.015(4)$, $b = 20.215(5)$, $c = 13.120(3)$ Å, $\beta = 113.10(4)°$, $V = 2199(3)$ Å^3, $\rho_{calc.} = 1.818$ g·cm^{-3} for $Z = 2$. CA4 four circle diffractometer (Enraf-Nonius), graphite-monochromatized $Mo_{K\alpha}$ radiation, $2\vartheta = 3-48°$, corrected for Lorentz polarization and absorption. Structure solved by direct methods and refined by full-matrix least-squares to $R = 0.029$, 1578 independent reflections ($I \geqslant 3\sigma(I)$). Further details of the crystal structure investigation are available on request from the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, England on quoting the names of the authors and the journal citation.
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X-Ray Spectroscopic Studies of the Surface Species in Co–Mo–Al_2O_3 Hydrodesulphurization Catalysts

By *P. R. Sarode, G. Sankar, A. Srinivasan, S. Vasudevan, C. N. R. Rao*,* and *J. M. Thomas**

Despite a number of investigations of Co–Mo–Al_2O_3 hydrodesulphurization catalysts carried out in recent years[1], a clear understanding of the active sites in these catalysts has not emerged. Accordingly, we have carried out a systematic study of Al_2O_3-supported, sulphided cobalt-molybdenum (Co–Mo) catalysts and their oxide precursors over a wide range of compositions together with a number of model oxides and sulphides of cobalt and molybdenum, including several samples of Co-MoS_2. For this purpose, we have employed X-ray photoelectron spectroscopy (XPS) and X-ray absorption spectroscopy; in the latter, use was made of both X-ray absorption near edge structure (XANES) and extended X-ray absorption fine structure (EXAFS) to determine coordination numbers and bond distances. The present study shows that Co^{II} and Mo^{IV} are present as sulphides on the surfaces of the active catalysts, each in octahedral coordination; furthermore, our results indicate the presence of disulphide bonds which may play a significant role in the hydrodesulphurization processes.

Co–Mo–Al_2O_3 precursors with Co:Mo ratios between 3:12 and 6:12 exhibit Mo($3d_{5/2}$) binding energies of 232.3 ± 0.1 eV (XPS) and a 3d spin-orbit splitting of 3.1 ± 0.1 eV, characteristic of Mo^{VI} species. The Co($2p_{3/2}$) binding energy is 781.7 ± 0.1 eV with a 2p spin-orbit splitting of 16.0 ± 0.1 eV and a satellite structure separated by ca. 6.2 eV from the main peak, showing that cobalt occurs as Co^{II}. The spectroscopic transition energies determined by XANES spectroscopy are similar to those of Co^{II} and Mo^{VI} oxides. The 1s→nd transitions show that Co is tetrahedrally coordinated whereas Mo is octahedrally coordinated in these oxide precursors. EXAFS spectra of the 4:12 and 6:12 oxide precursors confirm these coordinations and yield Co–O and Mo–O distances close to 2.0 and 1.80 Å, respectively (corresponding distances in CoO and MoO_3 are 2.12 and 1.86 Å).

Sulphided Co–Mo–Al_2O_3 catalysts with Co:Mo ratios between 2:12 and 12:12 show Mo($3d_{5/2}$) and Co($2p_{3/2}$) binding energies (228.9 ± 0.1 eV and 778.8 ± 0.1 eV, respectively) characteristic of Mo^{IV} and Co^{II}. The Co^{II} spectrum shows no satellites. In addition to these Mo^{IV} and Co^{II} species, the sulphided samples generally exhibit additional features due to Mo^{VI} and Co^{II} which are similar to those found in the oxide precursors. The S(2p)/Mo(3d) intensity ratio in XP spectra in the sulphided catalysts increases with increasing Co concentration. The Mo(3d)/Al(2p) intensity ratio also increases as the Co concentration increases, in contrast to the oxide precursors.

XANES spectroscopy suggests an octahedral coordination for both Co and Mo in their catalytically active sulphided state, the spectral transition energies being close to those of CoS and MoS_2. These coordinations are also corroborated by our EXAFS measurements. The Co–S and Mo–S distances found by EXAFS spectroscopy are 2.32 and 2.29 Å, respectively (the Co–S and Mo–S distances in

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CoS, $(NH_4)_2MoS_4$, and MoS_2 are 2.39, 2.18, and 2.41 Å respectively).

We have estimated surface compositions of the 4:12 and 6:12 sulphided catalysts using known photoelectric cross sections by assuming the presence of Mo^{IV} and Co^{II}. The compositions thus found generally show the presence of an "excess" of sulphur. The average surface compositions of the 4:12 and 6:12 catalysts are $CoMo_6S_{22}$ and $CoMo_2S_{10}$, respectively. If the excess sulphur is present as disulphide, the two compositions conform to the general formula $CoMo_{2n}(2n+3)S_2^{2-}(2n-2)S^{2-}$.

While some of our results on the sulphided Co–Mo catalysts are in accord with earlier reports in the literature[2–4], what is significant is the possible presence of S_2^{2-} ions on the surfaces of dehydrosulphurization catalysts. Since it seems certain that octahedrally coordinated Co and Mo are present as 2^+ and 4^+ ions, respectively, we suggest that Co at the edges of MoS_2 sheets[5] favors the formation of disulphide linkages. The disulphide ion would be stabilized since the $Mo(d_{z^2})$ band is at a higher energy than the disulphide $3p^6$ band[6]. The S^{2-} $(3p^6)$ band overlaps the highest filled d band in group VIII elements such as Co. Furthermore, group VIII cations do not form strong π bonds as in MoS_2 and would favor disulphide linkages which could well be implicated in pathways for the hydrodesulphurization reaction.

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Remarks on *Simon*'s Review Article "Intermetallic Compounds and the Use of Atomic Radii in Their Description"—Cell Dimensions of Phases with a Given Crystal Structure Do Not Generally Form a Homogeneous Data-Set

By *Erwin Hellner** and *William B. Pearson**

In general, the unit-cell dimensions of binary, intermetallic phases with a given crystal structure do not form a homogeneous data-set if the diameter of the component atoms is examined at high precision and attention is paid to the group and period of the component elements in the periodic table. This is demonstrated using examples of phases with the cubic $MgCu_2$- and $SiCr_3$-type structures. The reasons for, and consequences thereof, are noted.

We have read and discussed with much interest *Simon*'s appraisal[1] of atomic radii and interatomic distances in intermetallic and other phases. However, with respect to one of the main aspects of his paper, we feel obliged to emphasize the results of some of our studies[2–4]. In analyzing near-neighbor diagrams[5] for phases with the same structure type according to *Simon*, the general, implicit assumption is that the unit-cell dimensions form an essentially homogeneous set. This generally appeared to be plausible when such diagrams were introduced, and, within the bounds of the relative precision with which the plots were made, some useful "overviews" were obtained[5]. However, we now know that plots such as Figure 6 in *Simon*'s article do not represent a homogeneous data-set with general experimental scatter of data collected from various sources. If in plotting the cell dimension(s) of binary intermetallic phases M_xN_y with a particular structure against the diameter D_M of a variable component M (the other component N is fixed), the choice of M and N is made according to the group and period of the elements in the periodic table, quite a different picture emerges: Different slopes of a versus D_M (dimensional behavior) are observed depending on the selection of the component atoms[2]. Such plots, of course, have considerably higher precision; for example, Figure 1[6] shows the slopes for different groups of phases with the cubic $MgCu_2$ structure (part of the data-set of *Si-*

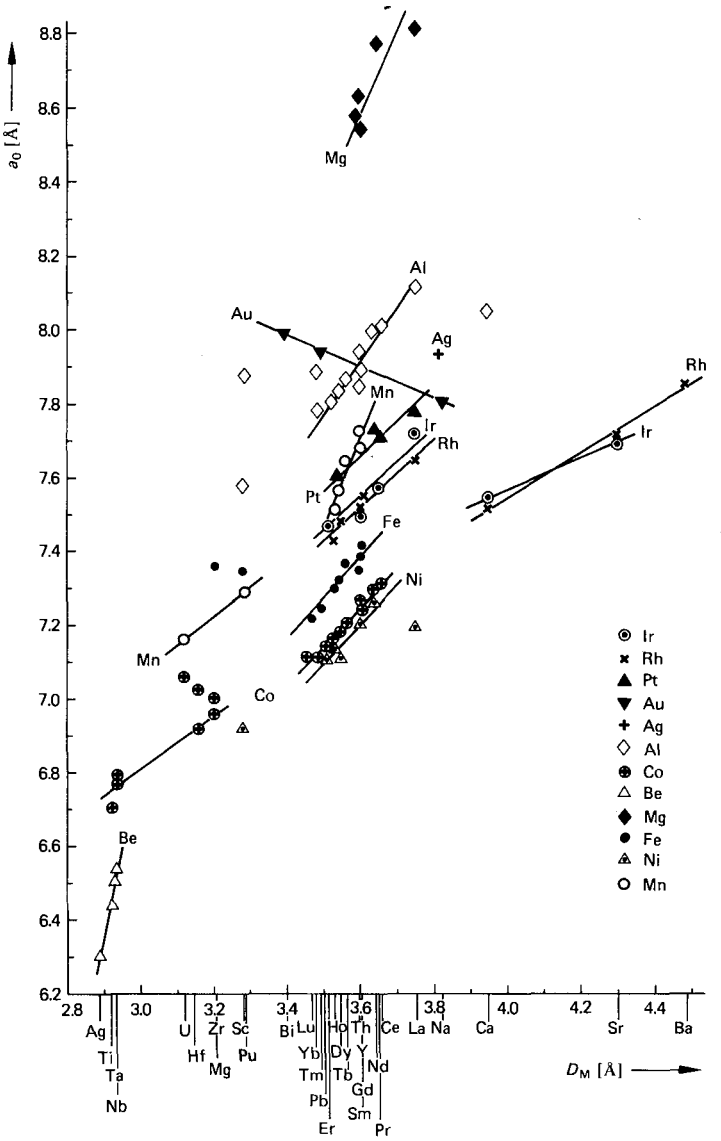

Fig. 1. Various phases (MN_2) with the cubic $MgCu_2$-structure. Plot of the unit-cell edge a_0 against D_M (diameter of the component M) for groups of phases that are formed by the same component N (indicated). The inhomogeneity of the data set is obvious.

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mon's Fig. 6, cf. [1]). These slopes vary from ca. 2.5 for lanthanoid/manganese phases to -0.4 for nonlanthanoid/gold phases.

Even when the unit-cell dimensions have been adjusted to ideal stoichiometry and the data-set appears to be extremely homogeneous as in *Simon*'s Figure 17[1], which reproduces *Waterstrat*'s data for MN_3 phases with the cubic $SiCr_3$ structure, the delusion may originate from the low precision or poor selection of the components in the plot. Indeed, *Simon* is not alone in this respect. Recently, but for different and justifiable reasons, *Villars, Girgis,* and *Hulliger*[7] obtained a linear relation between $d_{MN} = a \cdot \sqrt{5}/4$ and $\overline{R} = (R_M + 3R_N)/4$—essentially a versus D_M if N is fixed—calculated for 91 phases with a linear regression factor of 0.989; this would certainly be interpreted as indicating a homogeneous data-set. Nevertheless, with plots of much higher precision obtained using *Waterstrat*'s cell dimensions (i.e. the same data as *Simon*) *Pearson*[4] arrived at a different conclusion.

In these compounds the component N is a transition metal and M may either be a transition metal (T-T phases) or a nontransition metal (B-T phases). When these two groups are considered separately and a is plotted against D_M varying M and the phases of each component N are considered separately then:

1) The slopes of a versus D_M for the B-T and T-T phases of the same N components are not exactly the same; and
2) for both groups of phases the slope of a versus D_M decreases approximately linearly with increasing diameter of component N and is proportional to $-0.4\ (\pm 0.1)\ D_N$.

Conclusions: Taking two structural types as examples analyzed by *Simon*, we have shown that when the data are examined much more precisely and attention is paid both to the choice of the group and period of the components of the phases they may not form an overall homogeneous data-set in terms of dimensional behavior. The recognition of such inhomogeneities requires analytical methods to determine their causes: Indeed, for phases with the $MgCu_2$ structure inhomogeneities in dimensional behavior have long been recognized[8–10], but since the analyses were conducted using radius ratios no interpretation was possible.

- For phases of medium complexity and/or symmetry lower than cubic, the study of atomic volumes provides little more than overall energy considerations.
- Even plots of cell-dimensions a (b, c) against the diameters of the component atoms D_M or D_N are insufficiently diagnostic.
- However, plots of individual interatomic distances relative to the corresponding sums of the atomic diameters (for CN = 12 regardless of the atomic coordination number in the structure[11]) against the atomic diameters D_M or D_N indicate the basic causes of the different dimensional behavior for specific groups of phases with a given structure. These differences do not result per se from the various diameters of the component atoms but from the different interatomic contacts, or combinations thereof, which control the cell dimensions of groups of phases exhibiting different dimensional behaviors. Such information, which is quantitative in nature, should be amenable to firm theoretical analysis (see e.g. data in [12] and [13]).

Our studies also show that in three-dimensional space with D_M and D_N for CN 12 as abscissae and the cell dimension as ordinate all phases with a given structure lie on a planar surface. One exception to this rule has been noted—phases with the $SiCr_3$ structure discussed previously. These phases lie on a curved surface in D_M, D_N, a-space; nevertheless, this surface has the property that phases formed by the same component N and T or B as components M lie along straight lines on it.

Finally, we draw attention to potential difficulties in analyzing near-neighbor diagrams sketched with high precision[14].

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Intermetallic Compounds and the Use of Atomic Radii in Their Description—Reply

By *Arndt Simon**

The important remark made by *Hellner* and *Pearson*[1] that phases of one structure type to not represent a homogeneous set is further supported by the occurrence of (1st order) phase transitions which do not involve a change of structure type[2,3]. With this in mind, I stated in my review[4] "that it is not very meaningful to start an analysis of packing effects in a particular structure type on the basis of *all* known representatives". The Laves phases KNa_2, $CsNa_2$ and CsK_2 offer a model system—metallic bonding without significant heteropolarity—to study packing effects. The analysis yields a kind of Vegard rule, i.e. the distances between the atoms are proportional to the sum of atomic radii weighted according to the composition. On this basis, by means of a general approach for the adaption of atomic sizes to coordinations, the interatomic distances in the three phases can be calculated with high accuracy (3‰).

According to *Churcher* and *Heine*[5], such a Vegard-type law can only be plausible when certain assumptions about the interatomic potentials are made; but these assumptions are consistent with the relation between distances and force constants, according to *Badger*'s rule[6]. It must therefore be expected that many intermetallic compounds with topologically close packed structures obey such a Vegard-type law reasonably well. The alkali metal compounds mentioned follow this law extremely well, but all Laves phases of the $MgZn_2$ and $MgCu_2$ type are also reasonably well described by it (Fig. 6 in [4]), at least better than by a

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simple sum of atomic radii ($r_M + r_N$). Nevertheless, the deviations and scatter of the data are significant. In part, they were discussed and by no means were they taken to arise from a "general experimental scatter of data collected from various sources". On the contrary, it is repeatedly pointed out[4] that this scatter is due to interesting influences of chemical bonding. One cannot expect compounds like $CaRh_2$, $SrIr_2$, $AuBi_2$, or $NaAu_2$ to exhibit the same dimensional behavior as KNa_2. A subdivision of compounds into single families as shown in Figure 1[1] and their analysis according to *Hellner* and *Pearson* provides hope of gaining insight into the chemical bonding in these compounds; more precisely, into interatomic potentials and mutual influences of atomic sizes. The same insight might hopefully be gathered from analysis of the deviations of real compounds from Vegard-type behavior, which can be formulated quantitatively.

What does "radius ratios ... are intractable" mean? Radius ratios (r_M/r_N; since $2r = D$, also D_M/D_N) are as good (or bad) as the anticipated atomic sizes D_M and D_N, respectively. These depend on the structure and on the bonding partner. This is clear if the transition of a metal from body centered cubic to face centered cubic packing, on the one hand, and the different sizes of the Cs atoms in CsF and CsK_2, on the other, are considered. Therefore, all representatives in [1], but also in [4] are based on normalized values D_M, D_N for the close-packed elements. We are left with the problem of using near-neighbor diagrams for the representation of all compounds belonging to one structure type[4]. *Hellner* and *Pearson* prefer plots of the lattice constants against D_M or D_N, and they use the experimental distances d_{MM}, d_{NN}, d_{MN} (relative to the normalized values D_M, D_N, or 0.5 $(D_M + D_N)$, e.g., $(D_M - d_{MM})$) instead of the lattice constants for structures with free parameters. The representation $(D_M - d_{MM})/(D_N = f(D_M/D_N)$ chosen in [4], of course, corresponds to the representation of the linear relationships in Figure 1[1], but with a different scale since D_N is a constant for each of these relationships. The problem lies not in the use of near-neighbour diagrams, but in the interpretation of the plot of experimental data. The interpretation given in [4] has a distinctly different basis than previous interpretations[7].

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BOOK REVIEWS

Ozonation in Organic Chemistry. Vol. 2: Nonolefinic Compounds. By *P. S. Bailey*. Academic Press, New York 1982. xx, 497 pp., bound, $ 28.50.

"The saga of the many-faceted, many-splendored reactions of ozone with organic groupings is the purpose of this volume". Four years after Vol. 1[*], which deals with the ozonation of olefins, the author presents Vol. 2, which covers the literature until 1980 with 1249 citations.

A small chapter on the still underdeveloped ozonation of the *CC triple bond*—10^4 times slower than that of similarly substituted double bonds—is followed by four chapters dedicated to *aromatic compounds*. The author distinguishes between "bond attack" (O_3 as 1,3-dipole) and "atom attack" (O_3 as electrophile). The justification for applying the Criegee mechanism of olefinic ozonation to the aromatic compounds stems, inter alia, from the interception of the intermediate carbonyl oxides by methanol or acetic acid. These trapping reactions offer preparative access to dialdehydes starting from condensed aromatic systems.

The interaction of ozone with *nucleophiles* (amines, phosphites, thioethers and polysulfides) is the topic of a major chapter. The oxidation of the side chain as well as the oxide formation at the nucleophilic center are interpreted via the same O_3 adduct.

The reaction of ozone with CH and CH_2 groups is comparatively slower than with π systems, providing *tert*-alcohols and ketones, respectively. The initiating step of this important method (235 lit. ref.) is supposed to be a 1,3-dipolar CH insertion with partial carbonium character in the transition state; in superacid medium this insertion is ascribed to the species HO_3^+.

The *technique of ozonation* has made progress. The use of nitrogen as a carrier gas combined with the measurement of O_2 generation is an important analytical tool. In this operation, the ozone adsorbed on silica gel at $-78\,^\circ C$ is driven out by N_2. The "dry ozonation" on silica gel is likewise applied with increasing frequency. Quite justly the author pleads that most synthetic chemists are not sufficiently aware of the advantages of ozone as a reagent. The sewage purification with ozone and the controversy about the stratospheric ozone layer are briefly outlined.

The concluding chapter "Ozonation of Olefins Revisited" reports on the progress achieved (120 lit. ref.) since publication of Volume 1. Among other things, it is noteworthy that an ozonide has been found as a natural product in a fern. Dioxiranes, i.e., the cyclic isomers of carbonyl oxides, have been established at low temperature. The trump card that quantum chemists have predicted this species, is perhaps not so impressive; according to all MO or

VB calculations—except the most sophisticated ones—O_3 should possess the cyclic structure too.

Ozone participates in smog formation. This is the reason why ozonation in the gas phase was developed mainly by kineticists and ecologists. The embarrassing assumption that ozone reacts with hydrocarbons in the *gas phase* in a fundamentally different way than in solution, is becoming extinct. The introductory 1,3-dipolar cycloaddition and the subsequent 1,3-dipolar cycloreversion appear to be the same in gas and liquid phase. It is only the recombination of carbonyl oxide and carbonyl compound forming the ozonide which is replaced in the gas phase by unimolecular conversions of the carbonyl oxide and secondary reactions.

Grousing about a monograph meeting such high standards would be bad style. The quality of presentation deserves recognition. Statements about temperature, solvent and yields on the reaction arrows of the excellent formula blocks would be valuable for the reader. The "diradical structures" in the language of quantum chemists are sometimes falsely associated with reactivity by organic chemists. The notion of the carbonyl oxide occurring as a diradical in the gas phase and as a zwitterion in solution (p. 31) should not be taken verbally.

Whoever has to do with ozonation will find enlightening information in this standard work of reference written by one of the foremost leaders in the field.

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Protein Folding. By *C. C. Ghélis* and *J. Yon*. Academic Press, New York 1982. xiii, 562 pp., bound, $ 74.50.

The present state of protein structure research is marked by the completed crystal structure analyses of more than one hundred proteins, the elucidation of the mechanism of transcription and translation, as well as the possibilities for the sequencing of proteins and (recently) also the nucleic acids coding them. The result of all this is knowledge concerning the topology and detailed three-dimensional structure of globular protein molecules down to the atomic level and the insight derived therefrom into the catalytic mechanism of enzymes and into their evolutionary relationships.

Basically the functional state of proteins formed spontaneously both in vivo and in vitro represents the (kinetically accessible) state of minimum free energy. Both this structure itself and the process of its formation are described as "folding". It is the last stage in the "translation" of the genetic information stored in the nucleic acid into a covalent amino acid sequence and constitutes the last, largely unexplained, portion of the whole process of protein biosynthesis. Apart from the inborn curiosity of biochemists there are two reasons why interest is concentrated on this problem: Firstly, it is of theoretical importance, because, if the protein folding "code" were known, it would be possible, on the basis of the structure-function relationship, to use the nucleic acid sequences of otherwise uncharacterized proteins (enzymes) to predict their structures and their functions. Secondly, the "code" could be used to design molecules for the optimization of desired catalytic functions.

Both aims can only be envisaged because the three-dimensional structure of proteins is determined solely by the amino acid sequence of their polypeptide chains. This postulate made by *Crick* 25 years ago is based on the observation that protein molecules spontaneously revert to their native conformations after disturbance of their structure (denaturation) and are able to recover their biologically active state of association.

This present volume is devoted to the complex of questions outlined. It provides—apart from a volume of extended symposium contributions of the same name (Elsevier-North Holland, 1980)—the first comprehensive summary, and with its ca. 1500 literature references represents a veritable treasure trove for newcomers in the field.

The authors have attempted to describe the whole breadth and historical depth of the field, whereby they understand folding to have both systematic-descriptive aspects and energetic and kinetic ones. This leads to one of the weaknesses of the book, namely its length (and thus its price) together with a certain lack of criticality; the old and the new are presented side by side, with no attempt to sift and classify.

The book begins with a section on the intracellular environment and the significance of folding (30 pp.). Then follow almost 200 pages dealing with observations on the problem of protein folding from the viewpoint of the characterization of globular proteins. This is followed by 275 pages concerned with experimental methods; the book concludes with a 22-page summarizing commentary.

The above mentioned makeup and subdivision of the book cited and the relative sizes of its parts give some idea of the encyclopaedic proportions of the work. It is basically a detailed survey and not a more profound discussion of chosen examples. This has the consequence for the interested reader that every time "classical" portions of the subject are surveyed, the reader can obtain more detailed information first hand (from the presentations of *J. Richardson, Anfinsen* and *Scheraga, Baldwin, Creighton, Tanford* for example). The qualitative nature of the presentation is particularly regrettable for those parts of the field that become more and more accessible to a solid physicochemical treatment, e.g. intermolecular interactions (somewhat remarkably generally called intramolecular interactions), the structure of water, the thermodynamics and kinetics of unfolding and folding. Here it may also be a case of what the authors themselves call "progressing on shifting sand" with reference to rapidly evolving topics such as peptide processing, topogenic (not topogenetic) sequences and structural flexibility. The quality production of the book and the necessary time span before its appearance demand their price, particularly with respect to topicality.

In general the extraordinary amount of material and the documentation of even the older literature are of assistance to those who wish an effortless introduction to parts of the field. As previously stated a critical sifting of the material and tautening with respect to questions that still remain open would spare the reader some outdated matter. That the reading is not always simple, lies in the problem that "non-natives" who write in English frequently use an unorthodox idiom, that can sometimes only be completely understood after back translation. This remark is directed at the publishers rather than at the authors. This is not the case, however, with the subject index which is not really adequate for a book of this encyclopaedic nature.

It would be out of place here to criticize individual points; however, the occasional aesthetic or teleological

[*] Cf. *Angew. Chem. 91* (1979) 523; *Angew. Chem. Int. Ed. Engl. 18* (1979) 492.

arguments, the not always concise definitions, and the fuzzy distinction in some places between the thermodynamic and the kinetic viewpoint are mentioned as being symptomatic. Critical thinking is necessary on the part of the reader in order to avoid falling into error.

The book can be of good service as a reference work, both with regard to the various aspects of the subject and for particular topics. It is to be hoped that it will arouse biochemists and biophysicists to intensify research in one of the most interesting areas of physical biochemistry today.

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Organisch-chemische Nomenklatur. Einführung in die Grundlagen mit Regeln und Beispielen. 2nd edition. By *P. Fresenius*. Wissenschaftliche Verlagsgesellschaft, Stuttgart 1983. 280 pp., Paperback, DM 44.00.—ISBN 3-8047-0722-x

Lecture Notes in Biomathematics. Vol. 51: Oscillations in Mathematical Biology. Proceedings of a Conference held at Adelphi University, April 19, 1982. Series editor: *S. Levin*. Volume editor: *J. P. E. Hodgson*. Springer-Verlag, Berlin 1983. vi, 196 pp., Paperback, DM 32.50.—ISBN 3-540-12670-8

Corrigendum

The following corrections should be made to the communication entitled: "Reactions of Diphenyl(trimethylsilyl)phosphane with Alkyl(pentacarbonyl)manganese; Synthesis of the Ylide Complexes $(CO)_4MnCr(OSiMe_3)PPh_2$, and a New Driving Force for CO Insertion" by John A. Gladysz et al., Angew. Chem. Int. Ed. Engl. 23 (1984) 245:

The title should read: "Reactions of Diphenyl(trimethylsilyl)phosphane with Alkyl(pentacarbonyl)manganese; Synthesis of the Ylide Complexes $(CO)_4MnCR(OSiMe_3)PPh_2$, and a New Driving Force for CO Insertion". The heading to column 2 in Table 1 should read $\nu(C\equiv O)$.

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Electron Transfer between Metal Complexes— A Retrospective View (Nobel Lecture)**

By Henry Taube*

1. Introduction

This will be an account, in historical perspective, of the development of part of the field of chemistry that I have been active in for most of my professional life, the field that is loosely described by the phrase "electron transfer in chemical reactions". In the short time available to me for the preparation of this paper, I could not hope to provide anything significant in the way of original thought. But I can add some detail to the historical record, especially on just how some of the contributions which my co-workers and I have made came about. This kind of information may have some human interest and may even have scientific interest of a kind which cannot easily be gathered from the scientific journals. For publication there, the course of discovery as it actually took place may be rewritten to invest it with a logic that it did not fully acquire until after the event.

"Simple" electron transfer is realized only in systems such as $Ne/Ne^{\oplus}$. The physics already becomes more complicated when we move to $N_2/N_2^{\oplus}$, for example; and with the metal ion complexes which I shall deal with, where a typical reagent is $[Ru(NH_3)_6]^{2\oplus}$, and where charge trapping by the solvent, as well as within the molecule, must be taken into account, the complexity is much greater. Still, a great deal of progress has been made by a productive interplay of experiment, qualitative ideas, and more sophisticated theory, involving many workers. Because of limitations of space, I will be unable to trace all the ramifications of the field today and will emphasize the earlier history of the subject, when some of the ideas basic to the field were being formulated. This choice of emphasis is justified because, by an accident of history, I was a graduate student at the University of California, Berkeley, about the time the first natal stirrings of the subject of this article occurred, and at a place where these stirrings were most active. As a result, I may be in a unique position to deal knowledgeably and fairly with the early history of the subject. The emphasis on the early history is all the more justified because most of the topics touched on in this article, and also closely related topics, are brought up to date in a very recent volume of the series "*Progress in Inorganic Chemistry*"[1].

Chemical reactions are commonly classified into two categories: substitution or oxidation-reduction (redox). The latter can always be viewed as involving electron transfer, though it is agreed that when we consider mechanisms in solution electron transfer is not as simple as it is in the $Ne/Ne^{\oplus}$ case. Rearrangement of atoms always attends the changes in electron count at each center, and these must be allowed for. I will, however, simplify the subject by considering only processes where the chemistry is simple: those in which electron transfer leaves each of the reaction partners in a stable oxidation state. While substitution reactions can be discussed without concern for oxidation-reduction reactions, the reverse is not true. The changes that take place at each center when the electron count is altered are an essential part of the "electron transfer" process and may be the dominating influence in fixing the rate of the reaction. Moreover, most of the early definitive experiments depended on exploiting the substitution characteristics of the reactants and of the products. Thus, the attention which will be devoted to the substitution properties

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of the metal ions is not a digression but is an integral part of the subject.

An appropriate place to begin this account is with the advent of artificial radioactivity. This enormously increased the scope of isotopic tracer methods in chemistry and made it possible to measure the rates of a large number of redox reactions, such as that shown in eq. (a).

$$[^*Fe(aq)]^{2\oplus} + [Fe(aq)]^{3\oplus} \rightleftharpoons {}^*[Fe(aq)]^{3\oplus} + [Fe(aq)]^{2\oplus} \qquad (a)$$

(The first demonstration of a redox exchange was made by *von Hevesy* et al.[2], who used naturally occurring isotopes to follow Pb^{IV}/Pb^{II} exchange in acetic acid.) Because chemists there were involved in the discovery of many of the new isotopes[3], an early interest in this kind of possibility developed in the chemistry community at the University of California, Berkeley, and was already evident when I was a graduate student there (1937—40). In a review article on artificial radioactivity, *Seaborg*[3] mentioned an attempt[4] to measure the rate of $Fe^{3\oplus}/Fe^{2\oplus}$ exchange in aqueous chloride media, the result of this being that the exchange was found to be complete by the time the separation of Fe^{III} from Fe^{II} was made. It was appreciated by many that the separation procedure, in this case extraction of the Fe^{III} chloro complex into ether, might have induced exchange. It was also appreciated that chloride ion might have influenced the reaction rate, possibly increasing it, and that quite different results might be obtained were the experiment done with an indifferent anion.

There were several reasons for the interest among many physical-inorganic chemists in reactions such as described in eq. (a). That the interest in chemical applications of the new isotopes was keen in Berkeley may be traced, in part, to the involvement of much of the research body in teaching the introductory chemistry course. We all had a background of qualitative observations on simple oxidation-reduction reactions—such as, for example, the reaction of $[Ce(aq)]^{4\oplus}$ with $[Fe(aq)]^{2\oplus}$, gained from experience in qualitative or quantitative analysis. Still, to my knowledge, at the time I was a graduate student not a single measurement had been made of the rate of this kind of reaction. That a field of research, which has since grown enormously, was started by studying "self-exchange reactions"[5] such as in eq. (a), rather than net chemical changes ("cross-reaction")[5], may reflect the intervention of a human factor: Measuring the rate of a virtual process such as in eq. (a), today made commonplace for many systems by the introduction of new spectroscopic methods, seemed more glamorous than measuring the rate of oxidation of $[V(aq)]^{2\oplus}$ by $[Fe(aq)]^{3\oplus}$, for example. But I also recall from informal discussions that it was felt that driving force would affect the rate of reaction, and thus there would be special interest in determining the rates for reactions for which $\Delta G^0 = 0$ (except for the contributions to the driving force from entropy).

The interest in the measurement of the rates of self-exchange reactions I witnessed as a graduate student is not reflected in the literature of the years immediately following. Many of those who may have had plans to perform the experiments were engaged in war-related activities. After the war, at least five different studies on the rate of reaction (a), all carried out in non-complexing media, were reported, with conflicting results, some indicating a half-life for exchange on the order of days at concentration levels of 10^{-2} M. The discrepancies led to considerable controversy, and in informal discussions strong opinions were expressed on just what the true rate of self-exchange might be. The basis for this kind of judgment, exercised in the absence of any body of quantitative measurements, is worth thinking about. I believe it reflected an intuitive feeling that there would be a relation between the rates of self-exchange and of the related cross-reactions, and of course each of us had at least some qualitative information on redox rates for the $Fe^{3\oplus}/Fe^{2\oplus}$ couples. The definitive measurements on the rate of reaction (a) in non-complexing media were made by *Dodson*[6]. These measurements were soon extended[7] to reveal the effect of $[H^{\oplus}]$ and of complexing anions on the rate, yielding rate functions such as $[Fe^{3\oplus}][X^{\ominus}][Fe^{2\oplus}]$ (because substitution is rapid compared to electron transfer, this is kinetically equivalent to $[FeX^{2\oplus}][Fe^{2\oplus}]$ and to $[Fe^{3\oplus}][FeX^{\oplus}]$) in addition to $[Fe^{3\oplus}][Fe^{2\oplus}]$, but none specifying a unique structure for an activated complex. Particularly the terms involving the anions provided scope for speculation about mechanism. The coefficient for the simple second-order function was found[7] to be $4\,M^{-1}\,s^{-1}$ at 25 °C, $\mu = 0.5$, and those who had argued for "fast" exchange won out.

Another important experimental advance during the same period, important for several reasons, was the measurement[8] of the rate of self-exchange for $[Co(en)_3]^{3\oplus}/[Co(en)_3]^{2\oplus}$ (en = ethylenediamine) ($k = 5.2 \times 10^{-5}\,M^{-1}\,s^{-1}$ at 25 °C, $\mu = 0.98$). This was, I believe, the first quantitative measurement of the rate of a self-exchange reaction, and it may also have been the first time that the oxidizing capability of a cobalt(III) ammine complex was deliberately exploited. In this publication[8], the rate of the reaction of $[Co(NH_3)_6]^{3\oplus}$ with $[Co(en)_3]^{2\oplus}$ is also reported; this was, I believe, the first deliberate measurement of the rate of an electron transfer cross-reaction. In contrast to the $Fe^{3\oplus}/Fe^{2\oplus}$ system, where both reactants are labile to substitution, $Co(en)_3^{3\oplus}$ undergoes very slow substitution, and thus an important feature of the structure of the activated complex for the $[Co(en)_3]^{3\oplus}/[Co(en)_3]^{2\oplus}$ self-exchange appeared to be settled. In considering the observations, the tacit assumption was made that the coordination sphere of $[Co(en)_3]^{3\oplus}$ does not change on the time scale of electron transfer; hence, it was concluded that the activated complex for the reaction does not involve interpenetration of the coordination spheres of the two reactants. We were thus obliged to think about a mechanism for electron transfer through two separate coordination spheres ("outer-sphere" mechanism)[9].

In 1951, an important symposium on electron transfer processes was held at the University of Notre Dame, and the proceedings are reported in volume *56* (1952) of the *Journal of Physical Chemistry*. Though the meeting was organized mainly for the benefit of chemists, the organizers had the perspicacity to include physicists in the program. Thus, the complete gamut of interests was covered, ranging from electron transfer in the gas phase in the simplest kind of systems, e.g. $Ne/Ne^{\oplus}$, to the kind of system that the chemist ordinarily deals with. Much of the program was

devoted to experimental work, the chemistry segment of which included reports on the rates of self-exchange reactions as well as of reactions involving net chemical change—but none on cross-reactions. Two papers devoted to theory merit special mention: that by *Holstein*[10], whose contributions to the basic physics are now being applied by chemists, and the paper by *Libby*[11], who stressed the relevance of the Franck-Condon restriction[12] to the electron transfer process and applied the principle in a qualitative way to some experimental observations. It was clear from the discussion which several of the papers evoked that many of the participants had already appreciated the point which *Libby* made in his talk. Thus, in the course of the discussion, the slowness of the self-exchange in the aminecobalt complexes was attributed[13] to the large change in the Co–N distances with change in oxidation state, then believed to be much larger than it actually is. During the meeting, too, the distinction between outer- and inner-sphere activated complexes was drawn, and the suggestion was made that the role of chloride ion in altering the rate of the $Fe^{3\oplus}/Fe^{2\oplus}$ self-exchange might be that it bridges the two metal centers[14]. But, of course, because of the lability of the high spin Fe^{II} and Fe^{III} complexes no unique specification of the geometry of the activated complex can be made from the rate laws alone. During the discussion of *Libby*'s paper, a third kind of mechanism was proposed[15] involving "hydrogen atom" transfer from reductant to oxidant.

2. First Efforts

My own interest in the basic aspects of electron transfer between metal complexes became active only after I came to the University of Chicago in 1946. During my time at Cornell University (1941—1946), I had been engaged in the study of oxidation-reduction reactions, and I was attempting to develop criteria to distinguish between $1e^{\ominus}$ and $2e^{\ominus}$ redox changes. As an extension of this interest, I used $1e^{\ominus}$ reducing agents to generate halogen atoms and studied the ensuing chain reactions of the halogens with organic molecules. My eventual involvement in the study of electron transfer between metal complexes owes much to the fact that I knew many of the protagonists personally (*A. C. Wahl, C. N. Rice, C. D. Coryell, C. S. Garner*—the first two were fellow graduate students at Berkeley) and to the fact that I had *W. F. Libby,* with whom I had many provocative discussions, and *J. Franck,* as well as *F. H. Westheimer* as colleagues at the University of Chicago. By the time of the meeting at the University of Notre Dame (in which I did not participate), I appreciated in a general way the special advantages which the $Cr^{3\oplus}/Cr^{2\oplus}$ couple offered in the investigation of the mechanism of electron transfer and outlined my ideas to *N. Davidson* when he visited me en route to the meeting. But the experimental work which led to the first two papers[16,17] was not carried out until 1953. In the interim, I had failed to interest any of my graduate students in the work, because, of course, no one foresaw what it might lead to, and also because it seemed less exciting than other work in progress in my laboratory effects. The bulk of the work reported in these two papers was done with my own hands; I shall now outline the background to those early experiments.

My interest in coordination chemistry did not develop until I elected it as a topic for an advanced course given soon after coming to the University of Chicago. Instead of using the standard textbook material, I used as major source the relevant volume of "Gmelin" in which the chemistry of the cobaltammines is described. At this time, I already had a good background in the literature devoted to substitution at carbon and understood the issues raised in that context, and I soon became interested in raising the same issues for substitution at metal centers. Furthermore, it was evident that the complexes of metal ions which undergo slow substitution were readily amenable to experimental study. I became curious as well about the reasons underlying the enormous differences in rates of substitution for metal ions of the same charge and (approximately) the same ionic radii. The ideas that resulted were presented in my course the next time it was given, but the extensive literature study that led to the paper published in February 1952[18] was not done until 1949, when I was on leave from the University of Chicago as a Guggenheim Fellow.

In this paper, a correlation was made between electronic structure and mainly qualitative observations ("labile" complexes arbitrarily defined as those whose reactions appear to be complete on mixing and "inert" as those for which continuing reaction can be observed) on complexes of coordination number 6. In order to make the correlation, it was necessary to break away from the common practice in the USA of classifying complexes as "ionic" and "covalent" according to electronic structure. Thus, for example, comparison of the Cr^{III} with the high spin and thus "ionic" Fe^{III} convinced me that the bonds to the ligands might actually be somewhat more covalent in the Fe^{III} complexes that in the Cr^{III} complexes. Furthermore, it appeared to me that in earlier discussions of relative rates of substitution, where attempts were made to understand the observations in terms of the existing classification, there was a failure to distinguish between thermodynamic stability and kinetic stability. The affinity of $Cl^{\ominus}$ for $[Cr(aq)]^{3\oplus}$ is considerably less than it is for $[Fe(aq)]^{3\oplus}$, yet the rate of aquation of $[CrCl(aq)]^{2\oplus}$ is much less than it is for $[FeCl(aq)]^{2\oplus}$. Rates, of course, cannot be accounted for by considering ground state properties alone; the stability of the activated complex relative to the ground state must also be taken into account. When the effect of electronic structure on the relative stabilities is taken into consideration, a general correlation of rates with electronic structure emerges. (In the language of ligand field theory, for complexes of coordination number 6, substitution tends to be slow when in the metal ions each of the πd (non-bonding) orbitals, but none of the σd (anti-bonding) orbitals, is occupied. The rate constants for exchange of water between solvent and the hexaaqua ions of $V^{3\oplus}$ (πd^2), $Cr^{3\oplus}$ (πd^3), and $Fe^{3\oplus}$ ($\pi d^3\sigma d^2$) are $1\times10^3\ s^{-1}$, $5\times10^{-6}\ s^{-1}$, and ca. $1\times10^3\ s^{-1}$, respectively)[19].

A shortcoming of this early effort is that the rationalizations of the correlation offered were described using the

binding, because, when I wrote the paper, I did not understand the principles of ligand field theory even qualitatively. The VB approach provides no simple rationale for the difference in rates of substitution of labile complexes, which were found to cover a very wide range thanks to a pioneering study by *Bjerrum* and *Poulson*[20], who used methanol as a solvent to facilitate measurements at low temperatures, and those of *Eigen*[21], who introduced relaxation methods to determine the rates of complex formation of labile systems.

Activated complexes have compositions and structures, and it is necessary to know what these are if rates are to be understood. It is hardly likely that these features can be established for the activated complexes if they are not even known for the reactants, and in 1950 we were not certain of the formula for any aqua cations in water. It seemed to me important, therefore, to try to determine the hydration numbers for aqua cations. Hydration number as I use it here does not mean the average number of water molecules affected by a metal ion as this is manifested in some property such as mobility, but has a structural connotation: how many water molecules occupy the first sphere of coordination? Because the rates of substitution for $[Cr(aq)]^{3\oplus}$ were known to be slow[22], *J. P. Hunt* and I undertook to determine the formula for $[Cr(aq)]^{3\oplus}$ in water[23], with some confidence that we would be successful even with the "slow" method we applied, isotopic dilution using ^{18}O enriched water. That the formula turned out to be $[Cr(H_2O)_6]^{3\oplus}$ was no great surprise—although I must confess that at one point in our studies, before we had taken proper account of isotopic fractionation effects, $[Cr(H_2O)_7]^{3\oplus}$ was indicated, and, faced with the apparent necessity, I was quite prepared to give up my preconceived notions. It was also no great surprise that the exchange is slow ($t_{1/2}$ at 25°, ca. 40 h). Even so, the experiments were worth doing. They were the first of their kind and also attracted the attention of physical chemists, many of whom were astonished that aqua complexes could be as kinetically stable as our measurements indicated, and were impressed by the enormous difference in the residence time of a water molecule in contact with a cation compared with water molecules just outside. That we dealt with hydration in terms of detailed structure rather than in terms of averaged effects may have encouraged the introduction to this area of other methods, such as NMR spectroscopy, capable of making a distinction between cation-bound and free water[19]. As I will now detail, these hydration studies also led directly to experiments on the mechanism of electron transfer[16, 17].

3. The Inner Sphere Activated Complex

R. A. Plane undertook to measure the rate of self-exchange for the pair $[Cr(H_2O)_6]^{3\oplus}/[Cr(aq)]^{2\oplus}$ by using $[Cr(aq)]^{2\oplus}$ as a catalyst for the exchange of water between $[Cr(H_2O)_6]^{3\oplus}$ and solvent. The expected catalysis was found, but, owing to our inexperience in handling the air-sensitive catalyst, the data were too irreproducible to provide a value for the self-exchange rate. Catalysis on electron transfer was expected because the complex $[Cr(aq)]^{2\oplus}$ was known to be much more labile than $[Cr(H_2O)_6]^{3\oplus}$—the lability is now known[24] to decrease by a factor of at least 10^{14} when $[Cr(aq)]^{2\oplus}$ is oxidized to $[Cr(aq)]^{3\oplus}$ (note that $Cr^{2\oplus}$, but not $Cr^{3\oplus}$, has an antibonding electron). It occurred to me in the course of *Plane*'s work that it would be worthwhile to test the potential of the Cr^{III}/Cr^{II} couple as a diagnostic of mechanism with a nonmetal oxidant. Following up the idea, I did a simple test tube experiment, adding solid I_2 to a solution of $[Cr(aq)]^{2\oplus}$ which *Plane* had prepared for his own experiments. I observed that reaction occurs on mixing, that the product solution is green, and that this color slowly fades to produce one characteristic of $[Cr(H_2O)_6]^{3\oplus}$. The fading is important because it demonstrates that $[(H_2O)_5CrI]^{2\oplus}$, which is responsible for the green color, is unstable with respect to $[Cr(H_2O)_6]^{3\oplus}+I^{\ominus}$, and thus we could conclude that the Cr–I bond is established before Cr^{II} is oxidized.

The principle having been demonstrated with a nonmetal oxidant, I turned to the problem of finding a suitable metal complex as oxidant. What was needed was a reducible, robust metal complex with a potential bridging group as ligand, and the idea of using $[(NH_3)_5CoCl]^{2\oplus}$ surfaced during a discussion of possibilities with another of my then graduate students, *R. L. Rich*. Because at that time virtually nothing was known about the rates of reduction of Co^{III} ammines, and they were not considered useful oxidants, I was by no means sanguine about the outcome of the first experiment, which again was done in a test tube. I was delighted by the outcome. Reaction was observed to be rapid (the specific rate has since been measured[25] as $6\times10^5\ M^{-1}\ s^{-1}$ at 25°C), and the green color of the product solution indicated that $[(H_2O)_5CrCl]^{2\oplus}$ is formed. Further work[16, 17] showed that this species is formed quantitatively, and that in forming it picks up almost no radioactivity when labeled $Cl^{\ominus}$ is present in the reaction solution, thus demonstrating that transfer is direct, i.e., $Cl^{\ominus}$ bridges the two metal centers, and this occurs before $Cr^{2\oplus}$ is oxidized. The overall redox process can be described by eq. (b).

$$[(NH_3)_5CoCl]^{2\oplus} + [Cr(H_2O)_6]^{2\oplus} \underset{+H_2O}{\overset{-H_2O}{\rightleftharpoons}} [(NH_3)_5Co^{III}Cl\cdots Cr^{II}(H_2O)_5]^{4\oplus} \longrightarrow$$
precursor complex

$$[(NH_3)_5Co\cdots Cl\cdots Cr(H_2O)_5]^{4\oplus} \longrightarrow \quad \text{(b)}$$
activated complex

$$[(NH_3)_5Co^{II}\cdots ClCr^{III}(H_2O)_5]^{4\oplus} \xrightarrow{H_2O/H^{\oplus}}$$
successor complex

$$[Co(H_2O)_6]^{2\oplus} + NH_4^{\oplus} + [(H_2O)_5CrCl]^{2\oplus}$$

These early results were presented at a Gordon Conference on inorganic chemistry, which was held only a short time after they had been obtained, and they were received with much interest. *E. L. King* was present at the meeting, and together we planned the experiment in which self-exchange by an "atom" transfer mechanism was first demonstrated [eq. (c)][26].

$$[(H_2O)_5{}^*CrCl]^{2\oplus} + [Cr(aq)]^{2\oplus} \rightleftharpoons [{}^*Cr(aq)]^{2\oplus} + [(H_2O)_5CrCl]^{2\oplus} \quad \text{(c)}$$

Note that in a process of this kind, the bridging group will remain bound to a Cr^{III} center, but the auxiliary ligands about the original Cr^{III} center will be exchanged or replaced because of the high lability of Cr^{II}. (Several years later, *King* et al.[27] extended the self-exchange work to include other halides as bridging ligands and still later[28] encountered the first example of "double bridging" [eq. (d)].

$$cis\text{-}[(H_2O)_4{}^*Cr(N_3)_2]^{\oplus} + [Cr(aq)]^{2\oplus} \rightleftharpoons [{}^*Cr(aq)]^{2\oplus} + cis\text{-}[(H_2O)_4Cr(N_3)_2]^{\oplus} \quad (d)$$

A good case can be made for this also being the first demonstration of "remote attack", i.e., inner-sphere electron transfer where more than one atom separates the metal atoms in the activated complex.)

There was a brief hiatus in my work after the early experiments on inner-sphere mechanisms, caused by my taking leave from the University of Chicago in 1956. But before leaving, I hurriedly did some experiments[29], which, though semiquantitative at best, showed that not only atoms but groups such as $N_3^{\ominus}$, $NCS^{\ominus}$, and carboxylates transfer to chromium when the corresponding pentaamminecobalt^{III} complexes are reduced by $[Cr(aq)]^{2\oplus}$, and that there are large differences in rate for different dicarboxylate complexes (maleate much more rapid than succinate). Moreover, it was shown that in being oxidized Cr^{II} can incorporate other ligands, such as $H_2P_2O_7^{2\ominus}$, which are present in solution. In this paper the possibility of electron transfer through an extended bond system of a bridging group was first raised, but was by no means demonstrated by the results. During my leave of absence, *Ogard*[30] began his studies on the rates of aquation of $[(NH_3)_5CrX]^{2\oplus}$ (X = Cl, Br, I) catalyzed by $Cr^{2\oplus}$. By following the arguments made in connection with reaction (b), it can be seen that if an inner-sphere mechanism operates, $[(H_2O)_5CrX]^{2\oplus}$ and $NH_4^{\oplus}$ (acid solution) will be products. The contrast with uncatalyzed aquation is worth noting, where $[(NH_3)_5CrH_2O]^{3\oplus}$ and $X^{\ominus}$ are the expected products.

4. General Progress

The hiatus mentioned previously provides me with a suitable opportunity to outline some of the advances that were being or were soon to be made on other fronts. An important advance was that the rates of numerous self-exchange reactions were being measured. Here, I want especially to mention the contributions from the laboratories of *A. C. Wahl* and *C. S. Garner*. Some of the experiments by *Wahl* et al. made use of rapid mixing techniques—see, for example, the measurement[31] of the rate of self-exchange for $MnO_4^{1\ominus}/MnO_4^{2\ominus}$. An important experimental contributions was made by *N. Sutin*, who introduced the rapid flow method[32] (and later other rapid reaction techniques) into this field of study, and who helped others, including me, to get started with the technique. A spate of activity on the measurements of the rates of cross reactions followed, motivated to a large extent by the desire to test the validity of the cross-reaction correlation[5].

Attempts were being made by theoreticians to account for the barrier to reaction attending encounter and separation, and that contributed by charge trapping within the metal complex and by the surrounding medium. The papers which most influenced the experimentalists, at least during the formative period in question, were those by *Marcus*[33] and *Hush*[34] dealing with adiabatic[35] electron transfer. Other theoretical approaches were being advanced during this period, and, in some, attempts were made to account for nonadiabaticity; the various theories are compared and evaluated by *Marcus*[33]. (The current state of theory can be gathered from a recent article by *Sutin*[36].) Because this very important aspect of electron transfer reactions is not dealt with here, it is essential to mention that the processes occurring at electrodes were not being overlooked.

The correlation of the rates of cross reactions with the rates of the component self-exchange reactions[5] has been widely applied, especially to outer-sphere reactions. The limits of its validity were clearly set down by the author: allowance must be made for the work of bringing the reaction partners together and separating the products, electron delocalization must be great enough to ensure adiabatic behavior, but not so great as to materially reduce the activation energy. (The last condition, it should be noted, does not necessarily limit the applicability of the Marcus equation to outer-sphere processes.) *Hush*'s treatment[34] also leads to a correlation of rates of self-exchange and cross reactions, and also takes into account the contribution of ΔG^0. In fact, the first calculation of the rate of a cross reaction, shown in eq. (e),

$$[Pu(aq)]^{3\oplus} + [PuO_2(aq)]^{2\oplus} \rightleftharpoons [Pu(aq)]^{4\oplus} + [PuO_2(aq)]^{\oplus} \quad (e)$$

from the rates of the self-exchange processes and the equilibrium constant appears in [34].

More qualitative theory also profoundly influenced the development of the field, dealing with the question of how the choice of mechanism and relative rates are to be understood in terms of the electronic structures of the reactants. As is also true for rates of substitution, the observations are so sensitive to electronic structure that even qualitative ideas are useful in correlating observations and in pointing the way to new experiments. Early on, *Orgel*[37] applied qualitative ligand field theory to discussions of the inner-sphere mechanisms for the reduction of Cr^{III} and low spin Co^{III} complexes. When electron transfer takes place through a bridging group, it is important to distinguish a chemical or "hopping" mechanism—here a low-lying orbital of the ligand is populated by the reductant, or a hole is generated by the oxidant in an occupied orbital—from resonance transfer, i.e., electron tunneling through the barrier separating the two metal centers. This distinction was drawn rather early by *George* and *Griffith*[38], who moreover proposed alternative mechanisms for resonance transfer. Shortly thereafter, *Halpern* and *Orgel*[39] gave a more formal treatment of resonance transfer through bridging ligands. Concerns about the relation between electron structure and the observations on electron transfer strongly influenced my own work, but, before tracing this theme, I want to report on the progress made, mainly by others, in

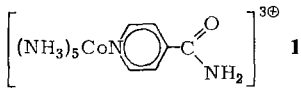
extending the descriptive chemistry of electron transfer reactions.

In a sense, the unambiguous demonstration of an inner sphere mechanism completed a second dimension in the field of electron transfer mechanisms. That in certain systems reaction perforce took place via an outer sphere mechanism had long been known, but until the experiments described in [16, 17] had been performed the inner sphere mechanism was only conjecture, and, as frequently happens in research in chemistry, only after conjecture, however reasonable, is upgraded by proof, is it accepted as a base for further development. That the distinction between the two reaction classes is meaningful, not only for chemical but also for kinetic aspects, will be illustrated by a single comparison: the rate constant of reaction of $[Cr(aq)]^{2\oplus}$ with $[(NH_3)_5CoCl]^{2\oplus}$ is ca. 10^8 greater than with $[Co(NH_3)_6]^{3\oplus}$[40] (the latter can only react by an outer sphere mechanism). The classification of reaction paths as inner sphere or outer sphere on the basis of rate comparisons, involving effects (such as those exerted by non-bridging ligands) established with reactions of known mechanism, became the focus of experiment and discussion when direct proof based on product or intermediate identification was lacking.

Early in the 1960s, new metal centers were added to the roster of those proven to react by inner sphere mechanism. For $[Co(CN)_5]^{3\ominus}$ as reducing agent[41], the demonstration of an inner sphere path again depended on the characterization of product complexes by orthodox means. *Sutin* et al. have been particularly resourceful in using flow techniques to provide direct mechanistic proof for reactions involving oxidizing centers ordinarily considered as labile to substitution: thus, note the proof of inner sphere mechanism for $[FeCl(aq)]^{2\oplus} + [Cr(aq)]^{2\oplus}$[42], $[CoCl(aq)]^{2\oplus} + [Fe(aq)]^{2\oplus}$[43], and even the much studied $Fe^{3\oplus}/Fe^{2\oplus}$ exchange[44]. It was appreciated early[17] that atom or group transfer is not a necessary concomitant of an inner sphere process. Whether the bridging group transfers to reductant, remains with the oxidant, or transfers from reductant to oxidant depends on the substitution labilities of reactants and products. Early qualitative observations[17] on the $[Cr(aq)]^{2\oplus} + [IrCl_6]^{2\ominus}$ system apparently exposed an example of reaction proceeding via an inner sphere mechanism, but which led to no net transfer of the bridging atom. Here, $[(H_2O)_5CrClIrCl_5]$ is formed as an intermediate, but this then aquates to $[Cr(H_2O)_6]^{3\oplus} + [IrCl_6]^{3\ominus}$ (later work[45] has shown that the inner sphere path is minor compared to the outer sphere, and that $Cr(H_2O)_\delta^{3\oplus}$ is the lesser product of the inner sphere path). Experiments[46, 47] with $[V(H_2O)_6]^{2\oplus}$ as reducing agent provided numerous examples of systems in which substitution at the reducing complex is rate determining for the net redox process (note that because of its electronic structure $[V(H_2O)_6]^{2\oplus}$ is expected[18] to undergo substitution relatively slowly). Unstable forms of linkage isomers were prepared by taking advantage of the chemistry of the inner sphere mechanism: $[(H_2O)_5CrSCN]^{2\oplus}$[48] by the reaction of $[Cr(aq)]^{2\ominus}$ with $[FeNCS]^{2\oplus}$[49]; $[(H_2O)_5CrNC]^{2\oplus}$[50] by the reaction of $[Cr(aq)]^{2\oplus}$ with $[(NH_3)_5CoCN]^{2\oplus}$. Oxygen atom transfer was shown to be complete[51] in the reaction of $[(NH_3)_5Co(H_2O)]^{3\oplus}$ with $[Cr(aq)]^{2\oplus}$. (The path involving direct attack on the aqua complex was later[52] shown to be unobservable compared to attack on the hydroxo complex; bridging by H_2O has, to date, not been demonstrated.) The inner sphere path was demonstrated[53] also for net $2e^{\ominus}$ processes in an elegant series of studies involving the reactions of Pt^{IV} complexes with those of Pt^{II}. In an important departure, *Anet*[54] showed that the "capture" property of $[Cr(aq)]^{2\oplus}$ in being oxidized can be exploited to produce complexes in which an organic radical is ligated to Cr^{III}. An entire chapter of the volume referred to in [1] is devoted to the chemistry of similar organochromium complexes[55].

5. Electronic Structure and Mechanism

A major theme in my own research on returning to the University of Chicago was to try to understand the large differences in rate, noted qualitatively in my early work[29], and later made more quantitative, for the reactions of $[Cr(aq)]^{2\oplus}$ with carboxylate complexes of $[(NH_3)_5Co^{III}]$. Many of the ligands were dicarboxylic acids, and, to explain the observation that when a conjugated π system connects the two carboxylates reaction is usually more rapid than it is for the saturated analogue, it seemed reasonable to assume that for conjugated ligands the reducing agent attacks the *exo*-carboxyl (remote attack), the conjugated bond system serving as a "conduit" for electron transfer. In adopting this view, the tacit assumption was made that the reactions are nonadiabatic, and hence the extent of electronic coupling would be reflected in the reaction rate. (In retrospect, this assumption is naive, because the effect of conjugation would be exerted even if the reducing agent attacked the carboxyl groups directly bonded to the metal center).



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A false start was made in demonstrating remote attack as defined here. Activation effects accompanying electron transfer were reported[56], which if true, would have constituted proof of remote attack for these systems. These effects could not be reproduced[57] in later work (I had by now moved from the University of Chicago to Stanford University). Remote attack with large organic ligands was finally demonstrated[58] in the reaction of **1** with $[Cr(aq)]^{2\oplus}$. This work, which also yielded a measurement of the rate of reaction of $[Cr(aq)]^{2\oplus}$ with the analogous Cr^{III} species, provided the clue to understanding, at least qualitatively, the differences in rate observed for different conjugated ligands. The astonishing result was that the rate of reduction of the Co^{III} complex is only about ten times greater than that of the Cr^{III} complex. When the bridging group is a nonreducible species such as acetate, the corresponding ratio is $> 10^4$. The insensitivity of the rate to the nature of the oxidant suggested that the electron does not transfer directly from Cr^{II} to the oxidizing center but that the mechanism rather involves the $1e^{\ominus}$ reduction[59] of the ligand by the strong reducing agent $Cr^{2\oplus}$, followed by reduction of the oxidizing center by the organic radical—i.e.,

a "hopping" mechanism. This view provided satisfactory rationalizations for most of the rates obtained with organic ligands. For example, that the rate is considerably greater for Co^{III}-fumarate complexes than for Co^{III}-acetate complexes may have little to do with the opportunity Cr^{II} has to attack the remote carboxyl in the fumarate complex, and only reflects the fact that fumarate can be reduced by $[Cr(aq)]^{2\oplus}$. Moreover, the otherwise puzzling observation that the rate for the fumarate complex is increased[60] upon addition of $H^{\oplus}$ is now easily understood; positive charge added to the ligand makes it easier to reduce. That many reactions of the class under consideration proceed by a stepwise mechanism has been convincingly demonstrated and amply illustrated in subsequent work, most of it carried out by *Gould* et al.[61].

The rationalization offered for the operation of the stepwise mechanism in the Co^{III}-Cr^{II} systems is that the carrier orbital on the ligand has π symmetry, while the donor and acceptor orbitals have σ symmetry. This makes it highly improbable that the four following conditions can be fulfilled simultaneously: Franck-Condon restrictions and symmetry restrictions at both centers. Whether or not this is the correct explanation, it led me to search for an oxidizing center among ammine complexes in which the acceptor orbital has π symmetry.

When the important condition that the complexes undergo slow substitution was added, only one couple within the entire periodic table, $Ru^{3\oplus}/Ru^{2\oplus}$ ($\pi d^5/\pi d^6$), qualified[62]. In principle, the $Os^{3\oplus}/Os^{2\oplus}$ couple is also a candidate, but unless some strong π acid ligands are present it is too strongly reducing to be useful. The ruthenium species had the added advantage that much more preparative work had been undertaken on them[63] and, further, that the redox potentials are close to those of the much studied cobalt couples. Since the π orbital on Ru^{III} can overlap with the π^* orbital on the ligand, we expected that the "hopping" mechanism would no longer apply. Reaction with $[Cr(aq)]^{2\oplus}$ is, in fact, much more rapid (2×10^4) than that of the Co^{III} isonicotinamide complex, and, moreover, the rates are quite sensitive to changes in the redox potential of the oxidizing center[64]. The chemistry also differs in an interesting way from that of Co^{III}/Cr^{II}. The bond between Ru and the ligand is not severed when Ru^{III} is reduced to Ru^{II}, and a kinetically stable binuclear intermediate is formed, as expected[18] from the electronic structures of the products—πd^6 for Ru^{II} and πd^3 for Cr^{III}.

Although the main intent of this article is to provide historical background rather than to develop the subject itself in detail, it may be appropriate in concluding this section to illustrate the strong dependence of the reaction properties on electronic structure with a few examples. Effects arising from differences in electronic structure are manifested in several different ways: by affecting the rates of substitution, they can influence the choice of mechanism, and, for an inner sphere reaction path, can determine whether binuclear intermediates are easily observable and whether there is net transfer of a group from one center to another; even after the precursor complex is assembled, orbital symmetry can affect the mechanism itself, as in the example mentioned previously, and can profoundly affect the rate of conversion of the precursor to successor complex.

The Cr^{III}/Cr^{II} ($\pi d^3/\pi d^3\sigma d^1$) and Ru^{III}/Ru^{II} ($\pi d^5/\pi d^6$) couples offer perhaps the greatest contrasts in behavior. It should be noted that the σ electron in Cr^{II} is antibonding, thus accounting for the tetragonal distortion in Cr^{II} complexes and their enormous lability compared to those of Cr^{III}. By contrast, the complexes of both oxidation states of ruthenium undergo slow substitution, with the useful exception of water as ligand, where the residence time on Ru^{II} is a fraction of a second.

The reducing agent Cr^{II} shows preference for an inner sphere mechanism, and this is especially marked if the acceptor orbital has σ symmetry. There is a great economy of motion for electron transfer by an inner sphere path for the σ donor-σ acceptor cases; this arises from the reciprocity at the two centers of the events required to overcome the inner sphere Franck-Condon barrier. This point is illustrated for the $[(H_2O)_5{*}CrCl]^2 + [Cr(H_2O)_6]^{2\oplus}$ self-exchange reaction in Figure 1, where the electronic levels are shown for the precursor complex, for the activated complex, and for the successor complex. Motion of the bridging chloride ion from Cr^{III} to Cr^{II} lowers the energy of a acceptor orbital on Cr^{III} and at the same time raises that of the donor orbital on Cr^{II}, and although other nuclear motions are also required, there is some correlation of the events required for activation to electron transfer, a correlation which is absent with an outer sphere mechanism. The high substitution lability of Cr^{II} of course means that the precursor complex can be formed rapidly.

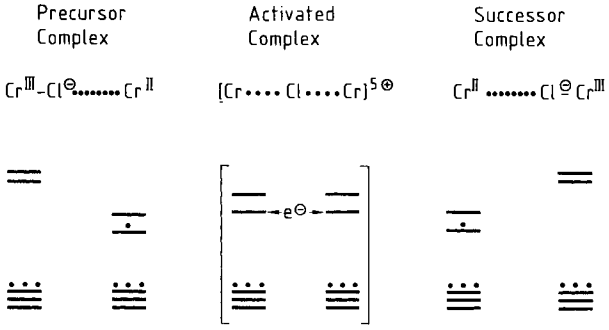


Fig. 1. Electronic structure and "atom" transfer in the self-exchange reaction $[(H_2O)_5CrCl]^{2\oplus} + [Cr(H_2O)_6]^{2\oplus}$.

Comparison of the rates of self exchange for $[Cr(H_2O)_6]^{3\oplus}/[Cr(H_2O)_6]^{2\oplus}$ and $[(NH_3)_5RuH_2O]^{3\oplus}/[(NH_3)RuH_2O]^{2\oplus}$ and how these respond when the higher oxidation state of each couple is converted into the hydroxo complex is quite instructive. The upper limit for the specific rate of self-exchange for the Cr^{III}/Cr^{II} couple is 2×10^{-5} M^{-1} s^{-1}[65,66]; although it has not been directly measured for the ruthenium couple, the specific rate can reasonably be taken to be close to that[67] for $[Ru(NH_3)_6]^{3\oplus}/[Ru(NH_3)_6]^{2\oplus}$, namely ca. 1×10^3 M^{-1} s^{-1}. Because the redox change for the ruthenium couple involves a π electron, it causes only a small change in the dimensions of the complex[68]. Thus, the Franck-Condon barrier to electron transfer arising from inner sphere reorganization is small, and facile transfer by an outer sphere mechanism is observed. By contrast, because Cr^{III} has no antibonding electrons and the electron added on reduction is antibonding, a

large change in dimensions and shape attending the reduction is observed, and the slowness of the self-exchange can be attributed, in part at least, to the inner sphere barrier[69]. Why the water molecule, which as a ligand on the oxidizing agent, which still has an electron pair available for sharing with the reducing agent, is such a poor bridging group is not yet understood.

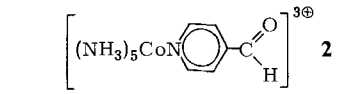
On deprotonation of a water molecule in each oxidant, the inner sphere path for the Cr^{III}/Cr^{II} system opens up, and a marked increase in rate is observed[65] ($k = 0.66\ M^{-1}\ s^{-1}$ at 25 °C)—the increase may be as large as a factor of 10^9[66]. The self-exchange rate for $[(NH_3)_5RuOH]^{2\oplus} + [(NH_3)_5RuOH_2]^{2\oplus}$ has not been measured, but it can be asserted with confidence that the rate via either an inner sphere path or an orthodox outer sphere path will be much less than it is for the aqua couple. The rate via the inner sphere path will be limited by the rate of bridge formation and thus will be no greater than $1 \times 10^{-2}\ M^{-1}\ s^{-1}$ (values of the order of $0.1\ M^{-1}\ s^{-1}$ for substitutions with neutral ligands on $[(NH_3)_5RuOH_2]^{2\oplus}$)[70]. The orthodox outer sphere path now has a composition barrier as well as a Franck-Condon barrier to overcome (the equilibrium constant for the formation of $[(NH_3)_5RuOH]^{\oplus}$ and $[(NH_3)_5RuOH_2]^{3\oplus}$ from $[(NH_3)_5RuOH]^{2\oplus}$ and $[(NH_3)_5RuOH_2]^{2\oplus}$ is ca. 10^{-9}). Reaction by "hydrogen atom" transfer[15] is a reasonable possibility, i.e., electron transfer concomitant with proton transfer from the Ru^{II} complex to the Ru^{III}, and some evidence in support of this kind of mechanism has been advanced to explain observations[71] made in the oxidation of $[(NH_3)_5RuOH_2]^{2\oplus}$ by $Fe^{3\oplus}$ and $[FeOH]^{2\oplus}$. Reaction by such a path might be quite facile and a rate in excess of $1\ M^{-1}\ s^{-1}$ would be strong evidence in its favor.

6. Applications of the Ru^{III}/Ru^{II} Couple

Some unexpected benefits have accrued from introducing Ru^{III}/Ru^{II} ammine couples to the study of electron transfer reactions. Ruthenium(II) participates in back bonding interactions to a degree unprecedented among the dipositive ions of the first transition series. A discovery[72] which forcefully brought this message home is that $[(NH_3)_5RuN_2]^{2\oplus}$ is formed in aqueous solution by the direct reaction of $[(NH_3)_3RuOH_2]^{2\oplus}$ with N_2. When the heteroligand in $[(NH_3)_5RuL]^{2\oplus}$ is pyridine or a derivative thereof, the complexes of both oxidation states undergo slow substitution, and by changing the number of π acid ligands a versatile series of outer-sphere redox couples is made available, spanning a range in redox potential of over 1 V. When derivatives of the Os^{III}/Os^{II} ammines are included, the useful range in aqueous solution is extended by approximately 0.5 V. These reagents are finding wide application in research on redox processes.

6.1. Intramolecular Electron Transfer

In order to arrive at a basic understanding of electron transfer processes, it would be a great advantage if the reactions could be studied intramolecularly rather than, as is commonly done, bimolecularly or intermolecularly, particularly if the geometrical relation between the two metal centers were unambiguously defined. Such systems had been encountered in studies of "induced" electron transfer[73]: when a powerful $1e^{\ominus}$ oxidant reacts with **2**, for example, the resulting coordinated organic radical can undergo intramolecular electron transfer, the oxidation of the ligand to the carboxylic acid being completed by Co^{III}. In some cases, intramolecular electron transfer can be intercepted by reaction of the radical with the external oxidant, but at best, only relative rates were obtained for these systems. In an elaboration of this kind of approach in which pulse radiolysis is used to convert the organic ligand to a radical—usually by reduction—intramolecular transfer rates can be measured[74]. These results are important in their own right, but are no substitute for experiments in which metal-to-metal electron transfer is studied.



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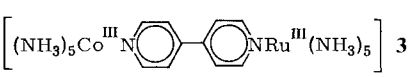

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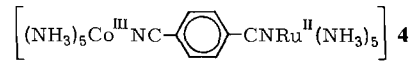
A strategy for dealing with the metal-to-metal case was devised[75a] which depends on the special properties of the Co^{III}/Co^{II} and Ru^{III}/Ru^{II} couples. The principle is as follows: When a complex[76] such as **3**, which has both metal centers in the oxidized state, is treated with an external reducing agent, Ru^{III} is reduced more rapidly than Co^{III}. This is a direct result of the differences in electronic structure, πd^6 and πd^5 for Co^{III} and Ru^{III}, respectively, the former requiring much more reorganization energy because the incoming electron is antibonding. In a subsequent step, Ru^{II} reduces Co^{II} in an intramolecular process, at least if the solution of the binuclear complex is sufficiently dilute.

The first synthesis[75a] of a $M_A^{III}\ M_B^{III}$ complex is rather ingenious, but it involves many steps and has the disadvantage that $SO_4^{2\ominus}$ rather than NH_3 is trans to the pyridine on Ru^{III}. *Schäffer*[77] has greatly simplified the preparative procedure by taking advantage of chemistry developed by *Sargeson* et al.[78], and has studied intramolecular electron transfer in **4** and in the related complexes with the ortho



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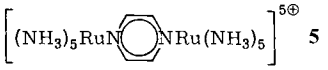
and meta isomers as bridging ligands. Quite independently of our work, *Haim et al.*[79] have carried out experiments similar to those described, but with $[Fe(CN)_5H_2O]^{3\ominus}$ as the reducing agent. Substitution at $[Fe(CN)_5H_2O]^{3\ominus}$ takes place readily, and hence the simple mixing procedure attempted by *Roberts*[75b] can often be used.

A point of interest in all of these studies was to learn how the rate of reaction responds to changes in the structure of the bridging group. For bipyridine complexes the coupling between the pyridine rings was therefore modified[76]; since the immediate environment about each metal

is left unaltered, the driving force for the reaction is but little affected, and changes in rate can then be attributed to changes in electronic coupling. The results obtained in studies of this kind are outlined in a recent review article by *Haim*[80]. Here, I will only mention an extension of this kind of strategy to a system of biochemical interest. *Gray* et al.[81] and *Isied* et al.[82] have succeeded in incorporating the $[(NH_3)_5Ru]$ group into cytochrome c at a position remote from the porphyrin (Ru^{III}-Fe^{III} separation: 15 Å). Different pulse methods were used by the two research groups to reduce Ru^{III} preferentially over Fe^{III}, and though the results of the two studies differ somewhat ($k = 20 \pm 5\ s^{-1}$ and $82 \pm 20\ s^{-1}$, respectively), it is clear that the general strategy is effective.

6.2. Robust Mixed Valence Molecules

The resurgence of interest[83] in the properties of mixed valence compounds can be traced to review articles[84–86] which appeared in 1967 and to the first deliberate synthesis of a robust mixed valence molecule, species **5**, which is commonly referred to as the Creutz-Taube ion[87]. (Quite



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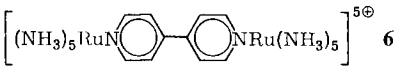
independently of our work, *Cowan* and *Kaufman*[88] prepared a molecule based on the ferrocenium/ferrocene couple.) *Peter Ford* and I first synthesized the Creutz-Taube ion in 1967. In undertaking its preparation, we were motivated by simple curiosity rather than by questions which might arise from a deep understanding of the issues raised by the properties of the mixed valence compounds. The fully reduced compound in the (Ru^{II}, Ru^{II}) state is readily prepared by direct substitution using pyrazine and $[(NH_3)_5RuOH_2]^{2\oplus}$, and, in carrying out the project, we were taking advantage of our knowledge of affinities and rates of substitution for both oxidation states of ruthenium. Complexes with Ru^{II} having a bond to a heterocyclic nitrogen atom show very strong absorption in the visible region of the spectrum ($\pi^* \leftarrow \pi d$)[89], and on observing that the color was not significantly altered when the (II,II) species is half oxidized, we did not pursue the matter further. Fortunately, *Carol Creutz* took up the subject again. The electrochemical results which she obtained in about June 1968 showed that the mixed valence state is very stable relative to the isovalent, and this suggested to us that electronic coupling in the mixed valence species is strong. At this stage, the review papers by *Hush*[85] and by *Robin* and *Day*[86] had appeared, and taking their content to heart, we felt certain that an intervalence band must exist, which *Carol Creutz* then located in the near IR ($\lambda_{max} = 1570$ nm), where, of course, it does not affect the color (hereto this region of the spectrum had been little investigated by chemists). Intervalence absorption corresponds to using the energy of a photon to transfer an electron from the reduced to the oxidized metal center, subject to the Franck-Condon restriction. Intervalence absorption confers the characteristic blue color to Prussian blue. The intervalence absorption occurs at longer wavelength for the Creutz-Taube ion than for Prussian blue, because the two iron sites in the latter are not substitutionally equivalent. Thus there is a compositional ground state energy difference attending electron transfer, which is then added to that associated with the Franck-Condon barrier when the process is induced by a quantum of light.

One of my main interests in the field of mixed valence molecules has been to explore and to try to understand the energetics of the systems. I will illustrate the kind of conclusion which we have reached in pursuing these interests, using the localized, mixed valence complex **6** as example, where we have relied on theory introduced by *Hush*[85] and *Mulliken* and *Person*[90], and by *Mayoh* and *Day*[91], the latter providing a correlation between the extent of electron delocalization and electronic structure[92].



6

The stability conferred on the ground state of **6** by charge delocalization is only of the order of 50 cal/mol, far below the upper limit of 5×10^2 cal/mol set by the electrochemical results, which measure the total stabilization of the mixed valent compared to the isovalent state. When the nuclear coordinates about each center are adjusted so that the Franck-Condon condition is met, the energy separating the bonding and antibonding states which arise from electron delocalization is calculated as 2.2 kcal/mol[93]. This is taken to be sufficient to ensure adiabatic transfer[94], in agreement with the conclusion reached in studies of intramolecular electron transfer in Co^{III}/Ru^{II} systems with 4,4′-bipyridine and related molecules as bridging ligands[76]. If electron transfer is assumed to be adiabatic, the specific rate for intramolecular electron transfer is calculated to be $3 \times 10^8\ s^{-1}$, in reasonable agreement with an estimate ($1.6 \times 10^8\ s^{-1}$) obtained from measurements of intermolecular electron transfer rates for pentaammine(pyridine)ruthenium complexes[95].

Mixed valence molecules have been prepared[96] which are delocalized even although the bridging group is so large that direct metal-to-metal orbital overlap cannot be responsible for the delocalization. These molecules have remarkably interesting properties in their own right, and are the subject of current studies[97].

7. Concluding Remarks

In this article, I have focussed rather narrowly on electron transfer reactions between metal complexes. The separation of this subclass from other possible ones which can be assembled from the reactant categories (metal complexes, organic molecules[98], molecules derived from other non-metallic elements, molecules in excited states[99, 100] or electrodes) is not as arbitrary as it might be were it dictated solely by limitations of space. Admittedly, all the possible electron transfer processes are governed by the same principles, at least when these are stated in a general way. But as these principles manifest themselves in the different subclasses, the descriptive chemistry can be quite different,

and these differences are the fabric of chemistry. The subclass treated has perhaps been the most thoroughly studied, yet, as the article by *Sutin* shows[36], our understanding at a basic level is far from complete. Even for the much studied $Fe^{3\oplus}/Fe^{2\oplus}$ self-exchange reaction [eq. (a)], which served to introduce this subject, the important question of whether or not the reaction is adiabatic has not been settled to everyone's satisfaction. Still, a great deal of progress has been made. The descriptive matter has increased enormously since 1940, and our understanding of it, both in scope and depth, has more than kept pace with observations. A great deal of progress has also been made in many of the other subclasses—for example, in the study of electrode processes and in "atom transfer" reactions (as a specific case the use of transition metal species to carry the oxidizing capacity of O_2 to a substrate such as an organic molecule). Both are of the greatest importance in industrial applications, and "atom transfer" reactions in providing an understanding of the chemistry of living cells. Because the subclasses are interrelated, progress in one speeds progress in another.

Many of the co-workers who have contributed to progress in the subject dealt within this article are cited in the references, and this is an implicit acknowledgment of their contributions. Because this account is incomplete, others who have contributed directly to this work have not been cited, nor still others who have had interests that are not reflected in the account I have given. I am grateful to them all for the help they have given, and for what I have learned in the course of working with them. The nature of the contributions made by my coworkers is not evident either from the acknowledgment I have made or from my expression of gratitude. I need to add that I have always relied on the independence of my co-workers, and to a large extent my contribution to the effort has been that of maintaining continuity.

I also wish to acknowledge financial support of my research by the agencies of the U. S. Government, beginning with the Office of Naval Research in about 1950. Later, I derived partial support from the U. S. Atomic Energy Commission, and still later from the National Science Foundation and the National Institutes of Health (General Medical Sciences). The Petroleum Research Fund of the American Chemical Society has also been a source of research support.

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$$\underset{\text{I}}{A\cdot B^{\ominus}} \longrightarrow \underset{\text{II}}{[A\cdot B^{\ominus}]} \longrightarrow A^{\ominus}\cdot B$$

State I is the precursor complex; in state II the energy is independent of whether the electron is on atom A or B, i.e., the Franck-Condon condition has been met. In adiabatic transfer, electron delocalization is great enough so that whenever state II is reached electron transfer can take place, and the rate of the chemical reaction is determined solely by the rate at which state II is reached. In nonadiabatic transfer, the system passes through state II a number of times before electron transfer occurs, and both the Franck-Condon barrier and the rate of electron transfer in state II are rate determining.
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"... to make Chemistry more Applicable and Generally Beneficial"—The Transition in Scientific Perspective in Eighteenth Century Chemistry**

By Christoph Meinel*

In 1751, the Swedish chemist *Johan Gottschalk Wallerius* first differentiated between "pure" and "applied" chemistry, a distinction which was quickly adopted by the other branches of science. Behind this was a new scientific concept of chemistry which emphasized the importance of applying chemistry's accumulated knowledge and its capabilities of providing for the general economic benefit. It also provided chemistry with a new position within the hierarchy of the sciences as well as with a new function in society. The reasons behind and causes of the change in scientific perspective associated with this concept point to the social and institutional conditions under which this field has developed into an independent academic discipline.

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1. The "Chemical Revolution"

During the Age of Enlightenment, chemistry broke with its humble role as an auxiliary adjunct science to medicine, to attain the position of a well-respected and even fashionable science, represented on the faculties of nearly all uni-

versities. The dynamics involved in this process have always attracted the attention of historians of science; for three aspects make this transition worthy of study.

Firstly, even though chemistry had made important practical and theoretical contributions, the "Chemical Revolution" occurred relatively late when measured against the developments in astronomy and physics from *Copernicus* to *Newton,* i.e. in relation to the "Scientific Revolution" as such. *Herbert Butterfield* consequently spoke of a "postponed scientific revolution in chemistry"[1], and strangely enough, the chemists of that time were very conscious of this. In the French Encyclopédie[2], which outranged all other contemporary works as the voice of the Enlightenment, *Gabriel François Venel* (1723—1775) recognized as early as 1753 the necessity of a "new Paracelsus" who would raise chemistry to the rank of a true science: "Il est clair que la révolution qui placeroit la Chimie dans le rang qu'elle mérite, qui la mettroit au moins à coté de la Physique calculée; que cette révolution, dis-je, ne peut être operée que par un chimiste habile, enthousiaste, et hardi, qui se trouvant dans une position favorable, et profitant habilement de quelques circonstances heureuses, sauroit réveiller l'attention des savans, d'abord par une ostentation bruyante, par un ton décidé et affirmatif, et ensuite par des raisons, si ses premières armes avoient entamé le préjugé"[2].

Secondly, the emancipation of chemistry had to do with a fundamental modification of theory. The generally accepted premise up to that time had been that all combustion phenomena could be explained by phlogiston, thought to be a volatile constituent of flammable materials. This theory was replaced by *Lavoisier*'s theory of oxidation. With the acceptance of this new theory, chemistry gained not only a comprehensive theoretical basis, but also a new terminology, making it literally impossible for supporters of the old and new schools of thought to understand one another. For this reason, *Thomas S. Kuhn* views this process as a typical example of scientific revolutions and, at the same time, as confirmation of his controversial thesis that advances in scientific development do not occur on a cumulative-evolutionary basis, but rather take revolutionary leaps and bounds, expressed in changes of paradigms[3]. *Kuhn* is in accord with the older literature on the history of chemistry, maintaining that it was just this replacement of the phlogiston theory by the oxidation theory, which was responsible for chemistry's breakthrough and subsequent scientific success. Developing *Kuhn*'s position, *Elisabeth Ströker*[4] recently examined the prerequisites for crisis and ramifications of this paradigm change on a more theoretically and historically differentiated basis; however, she is almost exclusively concerned with alterations in the cognitive area of chemical knowledge and theories, whereas *Kuhn* alluded to the social components in the process of scientific change.

It is this third aspect which makes the history of chemistry in the eighteenth century so fascinating. For not only did the entire social structure of the scientific community alter itself, but also the position of chemistry within the hierarchy of both the sciences and society was changed. Chemists began to see themselves as representatives of an independent academic discipline, experiencing the necessary acknowledgement from outside their field and forming regional or vernacular communities, enabling them to develop the common forms of scientific communication still in use today. Chemistry can lay claim to the fact that it produced the first specialized journal in a scientific field, published in 1778, and the first international scientists' gathering ever held, in 1786. Not long ago, *Karl Hufbauer* convincingly described this process of breaking away from the "République des Lettres", of its institutionalization, professional integration and communication, using as his example the German chemical community[5].

But neither the alteration of the central paradigm nor the change in the social structure of the scientific community can alone adequately explain the astonishing impetus experienced by chemistry in the eighteenth century. This can least of all be accomplished by means of the traditional allusion to *Lavoisier*'s reform, since pre-*Lavoisier* chemistry can only partially be identified with the phlogiston hypothesis, and in the post-*Lavoisier* period chemistry can only be associated to a limited extent relation to the oxidation theory. In "Elementa Chemiae" (Leyden 1732) by *Herman Boerhaave,* one of the most influential textbooks of its time, the term "phlogiston" does not appear. And as early as the first third of the nineteenth century the relationship between generic and specific properties of substances, an idea central to *Lavoisier*'s reform, had already been dismissed. It is important to note, however, that of the 46 chairs in chemistry not directly related to a medical discipline that were instituted during the eighteenth century in German-speaking countries alone, around 70% had been set up before 1790, a time when it was impossible to speak of any influence of *Lavoisier*'s revolution in Germany.

The rise, establishment, and evolution of sciences are, of course, also social developments which can be traced back to certain groups of scientists. Thus, the intrinsic development of chemical theories, knowledge, and capabilities accompany the crystallization of specific behavior patterns and strategies, the purpose of which is to form the social and institutional basis for their own activities. For this reason the "scientific community" should be understood within the context of argumentation and action in which cognitive elements and institutionalization strategies converge, generating the self-understanding, unity, norms, and values important for just this group on an disciplinary, social and institutional level[6]. I choose to call these collective relationships a scientific orientation complex in order to overcome the unserviceable antithesis of internal and external factors of scientific development, established in 1931 by the Marxist school of science history[7]. It can be demonstrated in the history of chemistry that it was just such a comprehensive orientation complex which in the middle of the eighteenth century experienced a fundamental re-orientation, establishing the direction critical to the evolvement and further development of the discipline.

2. The Status of the Field

The origins of chemistry as an academic discipline lie in the seventeenth century. The Paracelsians had introduced

the therapeutic application of chemical medicines, thereby founding the field of chemiatrics. In 1609 *Johannes Hartmann* (1568-1631) was vested with the first chair in this new area of study at Marburg University. The alchemical leanings of the landgrave no doubt played a part in his appointment. Two generations later this discipline was already to be found at numerous universities, functioning as an auxiliary adjunct to medicine.

Initially, of course, chemistry had no easy position. The representatives of academic science greatly mistrusted the air of alchemical obscurity surrounding it. More important, with chemistry a whole new type of science had penetrated the halls of the traditional educational institution, the University. For chemistry's real place was not at the rostrum, but in the laboratory, where, although no research and experimentation in the modern-day sense was conducted, the work was performed manually with a practical and purposeful intent. This stood in contrast to the other disciplines, including medicine, which supported the inveterate scientific ideal. The professor of chemistry, who first had to brush the soot and dirt from his lab apron before congregating with his more respectable colleagues from other faculties, was a figure who represented a striking contrast to the scholarly ideal of the baroque period, a man to whom in the most literal sense the taint of the non-academic, the crafts, and the unclean adhered.

This situation was not to change very quickly, for the low status of chemistry within the academic hierarchy was institutionally and structurally defined. Professorships exclusively devoted to one particular subject were unknown; instead, each faculty maintained its own specific hierarchy, where advancement was largely based on seniority; here the differences in remuneration as well as the possibilities for lucrative work on the side played no small role. Within the faculties of medicine, this almost always meant that the medical professor of lowest rank lectured on chemistry as well as on pharmacy, botany, or anatomy. As soon as the opportunity arose, this professor then naturally advanced to the next highest position, finally becoming Professor primarius and could then combine his subject with a profitable private practice or with a position as physician to the prince. This system of advancement, a relic from the medieval university, maintained itself long into the eighteenth century. As long as it existed, it prohibited the development of professorships devoted exclusively to one particular science, for a doctor could hardly afford to place his professional aspirations on one of the subordinate subjects.

The reason for chemistry's bad image obviously lay in the concept of science itself, this having concerned itself primarily with a speculative and contemplative scientific ideal, seeing the search for essential truths as its main purpose. Everything else belonged to the arts. Even such a first-class authority on chemistry as *Daniel Sennert* (1572-1637) denied chemistry the status of "scientia" and reserved the right of researching into the causes of natural phenomena to natural philosophy (physica) alone, limiting chemistry to the narrow field of preparative manufacture with the emphasis on a pharmaceutical objective. This judgement was to determine the image of the subject for a considerable time. In 1786 no less than *Immanuel Kant* was still of the opinion that chemistry could be "nothing more than a systematic art or experimental doctrine, but never become a true science, because the principles thereof are solely empirical, envisioning no a priori representation of perception"[8].

As long as the empirical acquisition of knowledge and practical laboratory work stigmatized the subject's general esteem, the road to the autonomous development of the discipline would remain a long one.

The chemists of the Enlightenment, therefore, did everything in their power to weaken the prejudice that their discipline was simply a practical craft, a kind of "ars mechanica", without scientific character. They most certainly had recognized that their own dilemma was not so much a result of inner disciplinary deficiencies as due to the institutional conditions peculiar to their field of study. In this way a special literary tradition of doctrinal publications developed, the goal of which was to solicit support for chemistry as a distinct science in its own right and to make a broader public conscious of its true value[9].

3. Pure and Applied Chemistry

Under the circumstances described here, doctrinal guidelines were formed for the further development of the discipline enabling chemistry to overcome its formalistic division into a theoretical science, on the one hand, and a practical handicraft, on the other, a distinction which was perceived as inhibiting further development; this was the distinction between "pure" and "applied" chemistry, which exists to this day[10]. Actually, this twin notion occurred for the first time in its modern-day sense in the field of chemistry. In the course of the nineteenth century it was adopted by the other sciences. This represented more than a change in terminology, however, and, more accurately, it originated in the desire to formulate a new scientific concept of chemistry in order to endow its level of knowledge and its capabilities with a new purpose. From this time on, the decisive factor in determining the relative worth of the field was not to be the type of work carried out, whether practical or theoretical, but rather the research objective itself and its relevance to society. In the case of pure chemistry, this goal was to delve into the causes and apparent laws governing natural phenomena related to matter; applied chemistry was to exploit these insights for the benefit of mankind by solving concrete everyday problems. The fact that both pure and applied chemistry were to closely ally theoretical reason with experimental practice was seen as an obvious prerequisite.

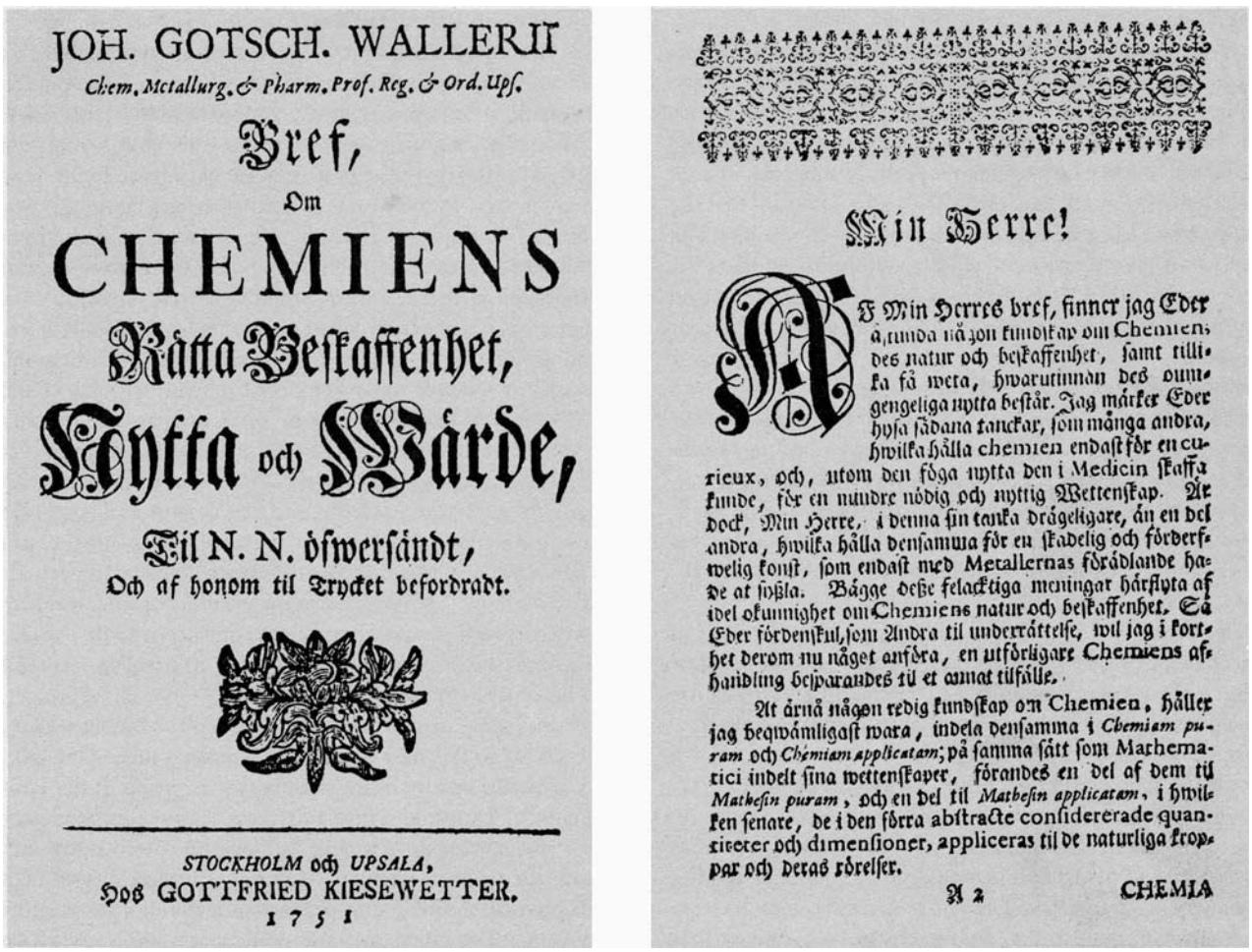
Fortunately, it is possible to pinpoint the circumstances which led to this new concept of chemistry more precisely. In 1749, the first chair of chemistry was set up at the University of Uppsala. Up to this time, lectures in chemistry had not existed in Swedish universities, despite the fact that this country, rich in mineral resources, exhibited a pragmatically oriented mineral-chemical and metallurgical tradition. The mines at Falun and their state assay office were well-known throughout Europe. The government commission responsible for the institution of the new chair

in chemistry had ordained the integration of the chair into the philosophical faculty, where students of the mining profession, as well as of economics and administrative science, obtained their general education. This was done, even though elsewhere in Europe chemistry was a self-evident part of the faculty of medicine. The appointment offer first went to *Georg Brandt* (1694-1768), director of the laboratory of the Board of Mines in Stockholm and assay master of the Royal Mint. Upon his refusal, the position was offered to *Johan Gottschalk Wallerius* (1709-1785), who had maintained a private chemical and metallurgical laboratory at the University of Uppsala from 1738. He was well-known, even outside Sweden, as the author of a handbook on mineralogy. In July 1750, *Wallerius* accepted his new position as the first professor of chemistry in Sweden. The rector of the University had requested him to expound on the reasons for bestowing the privileges of academia on chemistry in his inaugural lecture—at this time still a controversial topic!

Even though the manuscript of his lecture no longer exists, there is reason to believe that *Wallerius* answered the question in the affirmative, just as *Boerhaave*'s successor in Leyden, *Hieronymus David Gaubius*. In 1731 *Gaubius* had dedicated his "Oratio inauguralis qua ostenditur Chemiam artibus academicis jure esse inserendam" to just this topic and had also had it published. *Wallerius* knew this publication.

Among other duties, the new professor of chemistry was to hold lectures on chemistry, metallurgy, and pharmacy. However, he was also to examine the students of medicine in pharmacy, chemistry, and the art of writing prescriptions. The king himself had insisted that this examination be conducted by a chemist on the philosophical faculty. Understandably, the professors on the faculty of medicine felt this to be a scandalous infringement of their innate scientific and, of course, financial rights, for it meant their forgoing the not unprofitable examination fees, which reduced their not exactly lucrative salaries even further. The spokesman for their cause was none other than *Carl Linnaeus* (1707-1778). Originator of the modern classification system for plants and professor of botany, dietetics, and Materia Medica in Uppsala, he was also president of the Stockholm Academy of Sciences and physician to the king. Nevertheless, his objection remained unsuccessful. The professorship in chemistry stayed with the philosophical faculty, keeping its controversial examination privileges. Thus, its institutional framework was established.

In his autobiography[11], however, *Wallerius* recalls that initially no-one could form a true picture of just exactly what chemistry was. To publicize his field and further his



JOH. GOTSCH. WALLERII
Chem. Metallurg. & Pharm. Prof. Reg. & Ord. Upſ.

Bref,
Om
CHEMIENS
Rätta Beſkaffenhet,
Nytta och Wärde,
Til N. N. öfwerſändt,
Och af honom til Trycket befordradt.

STOCKHOLM och UPSALA,
Hos GOTTFRIED KIESEWETTER.
1751

Min Herre!

Af Min Herres bref, finner jag Eder åstunda någon kundskap om Chemien, des natur och beskaffenhet, samt tillika få weta, hwarutinnan des oumgengeliga nytta består. Jag märker Eder hysa sådana tanckar, som många andra, hwilka hålla chemien endast för en curieux, och, utom den föga nytta den i Medicin skaffa kunde, för en mindre nödig och nyttig Wettenskap. Ar dock, Min Herre, i denna sin tanka drägeligare, än en del andra, hwilka hålla densamma för en skadelig och förderfwelig konst, som endast med Metallernas förädlande hade at syssla. Bägge dessa felacktiga meningar härflyta af idel okunnighet om Chemiens natur och beskaffenhet. Så Eder fördenskul, som Andra til underrättelse, wil jag i korthet derom nu något anföra, en utförligare Chemiens afhandling besparandes til et annat tilfälle.

At årnå någon redig kundskap om Chemien, håller jag begwämligast wara, indela densamma i *Chemiam puram* och *Chemiam applicatam*; på samma sätt som Mathematici indelt sina wettenskaper, förandes en del af dem til *Matheſin puram*, och en del til *Matheſin applicatam*, i hwilken senare, de i den förra abſtracte conſidererade quantiteter och dimenſioner, appliceras til de naturliga kroppar och deras rörelſer.

A 2 CHEMIA

Fig. 1. In this "open letter" by *Johan Gottschalk Wallerius*, dated 10th August 1751, the new and promising distinction between Pure and Applied Chemistry was used for the first time. (Reproduced by permission of the Niedersächsische Staats- und Universitätsbibliothek, Göttingen.)

own cause, he had a small essay printed in Swedish in the form of a letter addressed to an unknown person, in which he introduced the true object of the study, as well as the use and value of chemistry, going into great detail (see Fig. 1). At the very beginning, *Wallerius* coined the conceptual distinction between "pure" and "applied" chemistry. The latter "Chemia applicata" was emphasized by him, and considering the previous events, it is hardly surprising that *Wallerius* was less concerned with the medical and pharmaceutical applications of chemistry than he was with its agricultural, metallurgical, and mineralogical uses, feeling that these areas held the highest economic promise.

Whereas the Swedish "Bref" was directed at students and the general public, *Wallerius* addressed a Latin dissertation "De nexu Chemiae cum utilitate Reipublicae" (Stockholm 1751) of the same year to the academic world and to those politically responsible for the country. Prefacing the work were no less than four Latin, Swedish, and French dedications to eminent personages. The main theme of this work, which was publicly defended by a certain *Lorenz Hiortzberg* under the chairmanship of *Wallerius,* was the distinction between pure and applied chemistry as well as the political and economic uses of the latter. Again, mineral chemistry and metallurgy were the fields in which the fruits of this science seemed closest at hand, while the profitability of chemical medicines was treated rather distantly. In view of the doubtful therapeutical successes achieved by the potent inorganic medicines then administered, this is certainly understandable.

The decisive factor which led to the acceptance and propagation of "pure and applied" chemistry was the general chemistry textbook by *Wallerius* ("Chemia Physica", Stockholm 1759), which he first published in Swedish and then personally translated into Latin, the language of academic Europe (Stockholm, 1760). Shortly thereafter, translations into German also appeared. This work played an important role in the history of chemistry textbooks in that it gave birth to a whole new generation of textbooks, written in the vernacular, the express purpose of which was to represent chemistry as an integral part of the physical natural sciences without reducing it to the level of medical or pharmaceutical interests. Its title "Chemia Physica" was intended to express just this general scientific concern. In this textbook *Wallerius* took the opportunity to develop his scientific concept of chemistry even further, for now he had realized that by consistently classifying the field in accordance with its objective and effect two things would occur: not only would the old separation of theory and practice lose weight, but so would the tiresome dispute over the definition of chemistry as a science or as an art. Instead, he regarded all subdivisions of applied chemistry as independent self-contained sciences which comprised both theoretical and practical aspects.

In choosing the twin concept "pure and applied" chemistry, mathematics had been openly declared as the model, although the mathematical terms had an entirely different meaning. "Pure" mathematics meant that part of the mathematical sciences which dealt with numbers only as intellectually perceptible, incorporeal patterns, whereas "applied" mathematics, according to the literal translation of "mathematica mixta", meant that part of mathematics which dealt with the numerical relationships of real things, perceptible to the senses. The aspect of utility and general benefit which has been connected with the concept of applied science since *Wallerius* was nowhere to be found in "applied mathematics" until the end of the nineteenth century. It is therefore worthy of attention, and most certainly no chance occurrence, that the modern definition of this twin concept originated in chemistry, thereafter spreading to all other sciences and European languages during the nineteenth century. The historical development of its influence will not be expanded upon here[12]. It should be mentioned, however, that the key role in its propagation was played by the Greifswald chemistry professor *Christian Ehrenfried Weigel* (1748-1831). Until 1815 the university at which he lectured was part of the Swedish Kingdom, so that as a result he was exceedingly familiar with the Scandinavian chemical tradition[13]. In addition to translating French and Swedish authors, he was also publicly active as a proponent of an autonomous chemical science by means of his own textbooks and popular writings. He was well-known among his contemporaries as the inventor of the water-jacketed condenser, which today is falsely known as *Liebig*'s condenser.

4. A Concept of Science in the Enlightenment

Wallerius' scientific concept of chemistry would not have been such a sudden and lasting success had it solely originated from a single Swedish chemist. In principle, the idea had been around for some time and it was *Wallerius* who merely succeeded in pinpointing and naming this new orientation of chemistry, which had reached a turning point around the middle of the eighteenth century. For almost simultaneously, it was possible to find *Mikhail Lomonosov* (1711-1765) making very related deliberations in Petersburg, in addition to the circle of authors of the French Encyclopédie. All of these are related by their common attempt to overcome the earlier contemplative ideal of science with its overrating of the theoretical, in order to replace it with a new bourgeois concept of science, which in turn contained the idea of progress and of actively molding the world. This new evaluation of chemistry and the higher status of its range of application was thus an inherent part of the purpose of the Enlightenment in putting rationality and the individual pursuit of happiness into social practice. The reason that this process began earlier and more noticeably in chemistry than in the other natural sciences lies in the fact that applied chemistry had already achieved undisputed successes; and due to its level of development, further useful discoveries could be expected.

Chemistry's understanding of its own role and its status was influenced more and more by utilitarian thought in the eighteenth century. Hardly an author wrote a new work without expressly informing the public of its far-reaching and direct benefits. Even textbooks were laid out according to the widely circulated "Elementa Chemiae" by *Boerhaave,* so that each "processus" was divided into "apparatus" (preparation) and "usus" (application). Seldom have rhetorical elements penetrated so deeply into the inner

structure of a discipline as in this case. Even in defining its objective and essence, the aspect of general benefit, as a rule, played a very important role in determining just what chemistry was. It would be premature to dismiss this only as rhetoric. Of course, it was also a question of safeguarding social and institutional support for their discipline, as well as obtaining new professorships, finances for a laboratory, or funds for an expensive experimental lecture. At the same time, it expressed chemistry's new understanding of its own function. The most respected representatives of the discipline made utilitarianism their own deep concern and stepped forth with treatises on the properties and preparation of foods and industrial goods, on questions of heating and lighting, dyeing and stain removal. It must be remembered that the first scientific publication of *Antoine Lavoisier,* then 21 years of age, was an answer to a question in a contest sponsored in 1764 by the Académie des Sciences as to the best and most economical method of lighting the streets of Paris at night. Working on a wide scale for the benefit of all was considered the final and utmost purpose of scientific work. *Ferdinand Wurzer* (1765-1844), one of the most productive German chemists of his generation, linked his professorship of chemistry and pharmacy at the University of Marburg with a teaching position at its Staatswirtschaftliches Institut, a school of economics. Consequently, he began the introduction to his "Handbuch der populären Chemie" (Marburg an der Lahn 1806) as follows: "People are finally beginning to generally realize how necessary chemistry is in order to handle crafts, factories and matters of economy more effectively, how industry with all its beneficial consequences has risen to an especially excellent level in those countries where knowledge of chemistry and its accomplishments are valued and utilized". And he concluded with this acknowledgement: "It is my deepest wish, with this work, to pay homage to that noble spirit of our time through whose power scientific knowledge is becoming less and less the monopoly of the learned, in that the majority of the latter are everywhere visibly attempting to work for the general benefit, to speak within the grasp of the masses, and to come down to their level"[13a].

Of course, the content of such popular treatises promising to be of directly beneficial use did not always fulfill what the flowery titles and prefaces foretold. Just the same, they must have had a considerable effect. By means of their thematic variety and high circulation, they reached an extraordinarily wide public from gentlemen farmers and manufacturers to ministerial officials. Thus the contribution this kind of scientific literature made to popularizing chemistry and to the public's acceptance of its rational and utilitarian image cannot be overvalued, even if the historiography of chemistry is all too partial to the development of theories and cognitive progress, disapproving of this kind of commercial literature.

5. Chemistry and the Economy

In the German tradition, chemistry's preoccupation with domestic and political economy as well as its leading role in stressing its economic benefit is especially marked. The reason for this is to be found in the discipline's very close ties to cameralism, the German variant of mercantilism, related to the administrative needs of small territories. The goal of the cameralists was the welfare of the state and the "best for all", to whose end mercantile thought and the national quest for power should strive. Their programme of economic reform envisioned increasing the working population as well as the government's intake of revenue by limiting imports and deliberately encouraging trade. By means of accessibility to and better exploitation of domestic raw materials and mineral resources, it was believed feasible to economically strengthen the country, if possible to the point of self-sufficiency. The initial cameralistic encouragement of industry, primarily due to government initiatives in the production of textiles, glass, and ceramics, achieved evident successes. As a result, new problems arose in the production and raw materials sectors, presenting a challenge to chemistry's professional competence.

Johann Joachim Becher (1635-1682), a very versatile man, known to chemists as the father of the phlogiston theory, was also one of the founders of cameralism and at a time when his chemical and alchemical works were almost forgotten, his contributions to cameralistics were still the accepted standard. In 1676 *Becher* founded his "Kunst- und Werkhaus" in Vienna, with the support of emperor *Leopold I,* who was greatly interested in alchemy. It was a technical teaching and research institute meant to enliven Austrian manufacturing methods. Obviously, a chemical laboratory, glassworks, and a metallurgical laboratory were included in its endowment, for encouragement of trade and technological development were accepted as the central mandate of modern government. Around the year 1700, *Georg Ernst Stahl* (1660-1734), the great theorist and respected teacher of a whole generation of German chemists, had expanded on *Becher*'s hypothesis of "fatty earth" to form the phlogiston theory and was thus able to account for a great number of chemical reactions. He had also adopted *Becher*'s doctrine of economically oriented chemical practice. The spiritual environment of Halle's Pietism, to which *Stahl* felt closely allied, had initiated a lively economic boom in that Prussian town even before the turn of the eighteenth century, a boom which resulted in the most modern forms of production and which influenced the building of factories, the establishment of *A. H. Francke*'s Foundations, and the transformation of the Saale into a navigable river. Last but not least, the University of Halle was also founded in this period (1694), to develop a short time later into the leading Prussian university of its time. That same year, *Stahl,* who came from Jena, was made Professor secundarius on the faculty of medicine in the ambitious, newly founded university. He distinguished himself there with treatises on chemical metallurgy, assaying, dyeing techniques and the extraction of saltpeter. His chemical-technical masterpiece "Zymotechnia Fundamentalis" (Halle 1697) laid the foundation for the chemical interpretation of such processes as the brewing of beer, alcoholic fermentation, and the preparation of vinegar. In the year of *Stahl*'s death, 1734, it was recommended by the translator of the German edition as a manual, with the aid of which a clever statesman could save millions in imports

by improving domestic production. It is noticeable that pharmaceutical and medical questions play a relatively minor role in *Stahl*'s chemical publications. His own medical system was based on an animist vitalism and therefore diametrically opposed to the iatrochemical school. *Stahl* believed that chemistry had little to contribute to a better understanding of the physiological and pathological processes occurring within the human organism. This conviction encouraged him to open up new areas of application for chemistry independent of medicine.

Later, it was none other than the Stahlians who carried on this impulse, freeing chemistry from its subordinate role as an auxiliary adjunct to medicine and attempting to integrate it into the economic-cameralistic doctrine of the modern state. The treasury's vital areas of interest made the relationship between economy, production, and science a most important objective of enlightened absolutist thought: mines and foundries, saltworks and porcelain manufactures, mint and glassworks, and finally the production of saltpeter for military purposes presented tasks enough for chemistry. Even the early cameralistics *(Kameralwissenschaft)* which originated from the domestic and rural economy, eventually recognized how much it could profit from chemically founded knowledge of substances and processes. *Johann Gottlieb Eckhardt*'s "Vollständige Experimental-Ökonomie" (Jena 1754) was one of the first works from the tradition of husbandry to apply scientific principles to farming, thus beginning a new epoch in agricultural science which was then to result in a still rather primitive type of agricultural chemistry, as set down in *Johan Gottschalk Wallerius*' "Åkerbrukets chemiska Grunder" (Stockholm 1761; also published in Latin, German, French, and English editions). The theoreticians and reformers of cameralistics in the eighteenth century consciously viewed knowledge of chemical science as a basic prerequisite of their discipline, demanding the establishment of independent teaching positions in chemistry in order to instruct government administration and department of finance employees. In Göttingen, then center of cameralistics in Germany, *Johann Heinrich Gottlob von Justi* (1717—1771), its most important systematist, held lectures on economy, polity and administration, but also on chemistry and mineralogy. In his "Staatswirthschaft", published in 1755, the classic textbook in this field, he demanded that an independent economics faculty be established, in which chemistry, natural history, mechanics, and politics should be instructed on a very practical level with emphasis placed on their social benefits.

It can again be assumed that Sweden was the model in this case, for there, the connection between chemistry and cameralistics had the oldest tradition[14]. As early as 1638, a state Assay Office had been set up in the Stockholm Mines Office, which controlled the education of mining officials as well as the Swedish mines and foundries and the analyses for the Royal Mint. Then in 1750, *Wallerius* was appointed to the first chair in chemistry on the philosophical faculty of the University of Uppsala to give special consideration of the economic interests of the country. Subsequently, the universities of Lund and Åbo linked their new chairs in chemistry to cameralistics and not to medicine. But later, even in Germany, professorships in chemistry existed on the newly-created *Kameralfakultäten* at Lautern/Heidelberg, Giessen, and Mainz.

6. The Emerging Academic Discipline

Thus, chemistry had conquered university territory, where it neither had to assert itself against the overpowering tradition of the medical faculties nor to defend itself against the charge of being only a handicraft. Instead, it could test its knowledge and capacities as a science in accordance with the interests of the respective governments. "To make the gifts of nature easier to use for human benefit", was the way *Johann Georg Menn* (1730–1781) put chemistry's real objective. "Is the real purpose of chemistry not clearly aligned with the most important intention of the State as a whole to work for the common good? Is it not also in agreement with the judgement of those who want nothing more than to see that those sciences prosper which are advantageous to each and every part of the state up to and including the tradesmen?"[15] The shift in orientation within the discipline with regard to its contents can also be followed by studying the change in interests of chemical publications in relation to questions of commercial application.

The persuasive power and success of the new doctrine can be explained by the fact that the capacities of eighteenth century chemistry with regard to knowledge of substances, theoretical interpretation, quality of apparatus and the technical ability to realize its objectives was a great deal better adapted to the new challenges posed by the fields of metallurgy, glass and ceramics manufacture, textile processing and dyeing; better, that is, than the much more complex questions in the medical and pharmaceutical traditions, as they had been posed by *Boerhaave*'s corpuscularian physiology and by the analysis and pharmacology of herbal substances, or by the chemo-cosmological doctrine of Paracelsism. Chemical theory was able to and was also permitted to prove itself, as this practical aspect now met with social approval and enjoyed official support. Chemistry's scientific and economic successes opened perspectives for its development into a profession and for its institutionalization as an academic discipline.

Of course, the ties to the medical faculties still existed, since future medical doctors made up by far the largest part of the students present at chemistry lectures. Only later was there a sudden increase in the number of students of pharmacy, primarily resulting from the introduction of new legal measures, which gave this area increasing importance as a breeding ground for the development of chemistry. Primarily institutional reasons therefore determined that the earliest efforts of the discipline, as "chemia physica" and as a part of general natural science, to break away from the medical faculty and become part of the philosophical faculty seldom met with lasting success. For, along with this transference, the right to examine medical candidates was almost always forfeited, resulting in the loss of a large number of the potential and paying students at lectures. For example, *Johann Friedrich Gmelin* (1748-1804) accepted a full professorship in chemistry on the

philosophical faculty in Göttingen in 1775, which was associated with extraordinary membership of the medical faculty. Three years later, however, he was forced to give up this position to accept a professorship on the medical faculty, despite the fact that his main scientific interests still lay in applied and industrial chemistry. *Friedrich Albert Carl Gren* (1760–1798) suffered a similar fate. He began as an assistant to the professor of mathematics and physics in Halle and was then employed from 1785 onwards as a teacher of political science and economics on the philosophical faculty of the university. In 1788 he accepted a full professorship in science and chemistry which, however, reverted to the medical faculty after a period of just a few months. Jena, with a student body of about 800, was then the third largest German university after Halle and Göttingen, and was simultaneously the first German university to make a lasting institutional differentiation between chemistry and medicine. Due credit for this farsighted appointment policy must be given to the minister responsible at the time, *Goethe*. In 1789 he established a professorship in chemistry, pharmacy and technology there, not without strong objections from the medical staff. He appointed *Johann Friedrich August Göttling* (1755-1809) to this position, an apothecary whom he had sent to study in Göttingen and England at government expense[16].

In surveying the development of chemistry in the eighteenth century, it can be noted that neither a mere improvement in external conditions nor a revolution in *Kuhn*'s sense had enkindled the far-reaching process of transformation enabling the field to liberate itself. In chemistry, the developing scientific community centered its attention not so much on a new and binding doctrine or theory as on a scientific orientation complex composed of rational argumentation and social action, which gave the discipline's level of knowledge and capacities a new direction; this provided chemistry with a more up-to-date form of institutionalization strategy and made a re-evaluation of its cognitive content possible. This shift in orientation equally influenced its objects of study and methods used, its formulation of objectives and self-understanding, its social role, and its institutional integration. At its turning point stood the concept of a "chemia pura et applicata", which set the stage for the autonomous development of the discipline about to take place.

7. Departure from the Chemistry of the Enlightenment

The historical development of chemistry as an academic subject, however, goes beyond its thus attained goal. The climax of the mutual approach of chemistry and cameralistics was reached by the first third of the nineteenth century. The doctrine, which had concentrated on general and economic benefit, had exhausted itself, especially since the hopes of obtaining immediate material advantage in this way were not fulfilled. Finally, the popularization of the subject by the movement started by the Enlightenment occasionally caused the original objectives to seem superficial and trivial. But also with regard to its content, eighteenth century chemistry had come to the limits of its theoretical and methodological capacities when attempting to answer the ever-increasing questions from physiological and organic chemistry which the research programme dealing with quantitative combustion analysis, having received some support from *Lavoisier's* elemental concept, was now at a loss to deal with.

The institutional hurdles had, however, been overtaken. Chemistry had established a firm foothold in the universities. It no longer required any support from outside. In addition, chemists, especially in Germany, influenced by Romantic *Naturphilosophie* as well as by the neohumanistic university reforms, which originated in Berlin in 1810, were increasingly attempting to sever themselves from their utilitarian heritage. The new guiding light was called "pure science", that is, insights gained for the purpose of knowledge and liberal education alone. Applied and technical chemistry had been elevated to the level of a university discipline, only, with a few exceptions, to again depart from the academic arena and regroup in polytechnics. No less a person than *Justus Liebig* (1803-1873), who came from a strong mercantile tradition of chemistry, propagated this new, solely research-oriented concept of education with amazing success and thus initiated a new shift of orientation within his discipline. His fierce attacks on proponents of the old line, including his own teacher *Karl Wilhelm Gottlob Kastner* (1738-1857), often overshot their mark and constituted a part of his campaign against the directly utilizable. The same is true of his polemic remarks on the plight of chemistry in Austria and Prussia, the two countries with the strongest mercantilist traditions: "Most of our statesman only know chemistry and physics as a result of the benefits they have reaped for industry and factories in foreign countries. It is, of course, natural to exploit these benefits; just as chemistry in earlier times was vassal to the doctor, so today it is used as a cog in the wheels of industry. ... It has never been regarded by the state as a means of intellectual education, as a natural science in the true sense of the word. A large number of the well-educated see chemistry consisting of certain simple rules, as an experimental art, useful for making soda and soap, in fabricating better iron and steel, in depositing solid colors on silk and cotton, but as research into nature it is unknown. How strange, then, that the expression education, as understood by the truly enlightened, only extends to include knowledge of classical languages, history, and literature! The question of the causes of natural phenomena and the changes occurring in everything that surrounds us in daily life is so well-adapted to the human spirit that the sciences which are supposed to supply satisfactory answers to these questions influence the cultural level of the mind more than all others"[17].

The challenge which originated in the *Humboldt* reform, with its overevaluation of the "humaniora" and in its new scientific ideal, was a part of chemistry from then on, and was answered in such a way that it held the seed of educational and scientific policy discussions up to the present day.

But let us recapitulate. When *Herman Boerhaave* (1668-1738) accepted the chair of chemistry at the University of Leyden in 1718, he complained anxiously that chemistry

was regarded as "uncouth, repulsive and tiring, excluded from the community of the learned, unknown or mistrusted by scholars; it was supposed to stink of fire, smoke, ash and rubbish, having hardly anything appealing to offer"[18]. Three generations later *Johann Friedrich Gmelin* (1748-1804), professor of chemistry at Göttingen, a supporter of the phlogiston theory and one of the first historians of his field, could already maintain, full of pride, that chemistry was "the idol before which all peoples, all classes, princes and subjects, clergy and secular, learned and unlearned, of high and low rank, kneel down; the favorite science of the great, the practice of which promised mountains of gold, quick reinstatement of ruined finances and of ruined health, ... the retreat of the wise searching for light and enlightenment; the most important aid to the researcher of nature, imparting knowledge to him where other sciences fail; the key to many of the secrets of nature; the chosen guiding light in the labyrinth of countless industries which nurture, bless and enrich people and states; the rational basis for the existence of foundries, of many factories, arts and handicrafts ..."[19].

Hardly eighty years had passed between these two assertions. During these years that far-reaching process of new orientation took place in chemistry, which first created the conditions necessary for its subsequent development as an autonomous academic discipline and for that change of paradigms, which we call the Chemical Revolution.

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[1] H. Butterfield: *The Origins of Modern Science, 1300-1800*, Bell, London 1957.

[2] *Encyclopédie ou Dictionnaire raisonné des Sciences, des Arts et des Métiers, Tome 3*, Briasson etc., Paris 1753, pp. 409–410. English translation of the quotation: "It is clear that the revolution that would place chemistry in the rank it merits would put it at least at the side of mathematical physics; this revolution, I say, can be carried out only by an able, enthusiastic, and bold chemist who, finding himself in a favorable position, and profiting ably from several fortunate circumstances, would know how to rouse the attention of learned men, first by a noisy ostentation, by a decided and affirmative manner, and then by reasons, if his first weapons would have subjugated prejudice."

[3] T. S. Kuhn: *The Structure of Scientific Revolutions (International Encyclopedia of Unified Science)*, University of Chicago Press, Chicago, IL 1962.

[4] E. Ströker, *Theoriewandel in der Wissenschaftsgeschichte—Chemie im 18. Jahrhundert*, Klostermann, Frankfurt am Main 1982.

[5] K. Hufbauer: *The Formation of the German Chemical Community (1720-1795)*, University of California Press, Berkeley, CF 1982.

[6] P. Weingart "On a Sociological Theory of Scientific Change" in R. Whitley: *Social Processes of Scientific Development*, Routledge & Kegan Paul, London 1974, p. 45-68.

[7] *Science at the Cross Roads*, Papers presented to the International Congress of the History of Science and Technology, London 1931, by the delegates of the U.S.S.R., Frank Cass, London 1931.

[8] I. Kant „Metaphysische Anfangsgründe der Naturwissenschaft [1786]" in W. Weischedel: *Immanuel Kant Werke, vol. 8*, Wissenschaftliche Buchgesellschaft, Darmstadt 1975, p. 15: „so kann Chymie nichts mehr als systematische Kunst, oder Experimentallehre, niemals aber eigentliche Wissenschaft werden, weil die Prinzipien derselben bloß empirisch sind und keine Darstellung a priori in der Anschauung erlauben."

[9] C. Meinel "De praestantia et utilitate Chemiae. Selbstdarstellung einer jungen Disziplin im Spiegel ihres programmatischen Schrifttums", *Sudhoffs Arch. 65* (1981) 366.

[10] C. Meinel "Theory or Practice? The Eighteenth-Century Debate on the Scientific Status of Chemistry", *Ambix 30* (1983) 121.

[11] N. Zenzén "Johan Gottschalk Wallerius' Självbiografi", *Lychnos Lärdomshist. Samf. Årsb. 1953*, 235.

[12] See also C. Meinel "Reine und angewandte Chemie. Die Entstehung einer neuen Wissenschaftskonzeption in der Chemie der Aufklärung", *Ber. Wissenschaftsgesch. 7* (1984), in press.

[13] C. Friedrich, H. Langer, H.-J. Seidlein "Christian Ehrenfried Weigel—Seine Bedeutung für die Entwicklung der pharmazeutischen Wissenschaft", *Pharmazie 37* (1982) 290, 446, 514.

[13a] Wurzer's original text: „Man fängt endlich an, es allgemein einzusehen, wie nothwendig die Scheidekunst sey, um Künste, Fabriken und Gegenstände der Oekonomie besser zu behandeln; wie Betriebsamkeit mit allen ihren wohlthätigen Folgen vorzüglich in jenen Ländern in einem ausgezeichneten Grade emporkommt, in welchen chemische Kenntnisse nach Verdiensten geschätzt und benutzt werden. ... Mein innigster Wunsch ist es, durch diese Schrift jenem edlen Geiste unserer Zeit zu huldigen, kraft dessen wissenschaftliche Kenntnisse mit jedem Tag weniger das Monopol der Gelehrten bleiben, indem die entschiedenste Majorität derselben sich sichtbarlich überall bestrebt, gemeinnützig zu seyn, für den großen Haufen verständlich zu reden, und sich zu seinem Gesichtskreis herabzulassen."

[14] H. Olsson: *Kemiens historia i Sverige intill år 1800 (Lychnos Bibliotek 17, 4)*, Almqvist & Wiksell, Uppsala 1971.

[15] J. G. Menn: *Rede von der Nothwendigkeit der Chemie*, Universitätsdruckerei, Köln 1777: „Ist ihr Zweck nicht ganz übereinstimmend mit der wichtigsten Absicht des gesammten Staates auf sein allgemeines Wohl, und auch mit dem Urtheil derjenigen, die nichts sehnlicher wünschen, als daß überall diejenigen Wissenschaften vorzüglich blühen, welche allen Gliedern des Staates und jedem besonders, bis auf den Handwerker einschlieslich, vortheilhaft sind?"

[16] H. Döbling: *Die Chemie in Jena zur Goethezeit (Zeitschrift des Vereins für Thüringische Geschichte und Altertumskunde, Neue Folge, Beiheft 13)*, G. Fischer, Jena 1928.

[17] J. Liebig "Über das Studium der Naturwissenschaften und über den Zustand der Chemie in Preußen [1840]" in J. von Liebig: *Reden und Abhandlungen*, Winter, Leipzig 1874, p. 12: „Die meisten unserer Staatsmänner kennen die Chemie und Physik nur aus dem sichtbaren Vortheil, den beide auf Gewerbe und Fabriken in fremden Ländern ausgeübt haben; es lag natürlich nahe, der nämlichen Vortheile sich zu bemächtigen; so wie die Chemie früher dem Arzte unterthan war, so benutzte man sie jetzt als Hebel der Industrie. ... Als Mittel zur Geistesbildung, als Naturforschung im eigentlichsten Sinne des Wortes, ist sie von dem Staate nie in Betrachtung gezogen worden. Eine Masse von ganz unterrichteten Leuten betrachten die Chemie als eine in Regeln gebrachte Experimentirkunst, nützlich, um Soda und Seife zu machen, ein besseres Eisen und Stahl zu fabriciren, um gute solide Farben auf Seide und Baumwolle zu liefern, als Naturforschung kennen sie sie nicht. Wie sonderbar, daß der Ausdruck Bildung bei einem wahrhaft erleuchteten Volke sich nur auf die Kenntniss der classischen Sprachen, Geschichte und Literatur erstreckt! Die Frage nach den Ursachen der Naturerscheinungen, den Veränderungen von allem, was uns täglich umgiebt, ist dem regen menschlichen Geiste so angemessen, daß die Wissenschaften, welche befriedigende Antworten auf diese Fragen geben, mehr als alle anderen, Einfluss auf die Cultur des Geistes üben."

[18] H. Boerhaave: *Sermo academicus de Chemia suos errores expurgante*, P. v. d. Aa, Leyden, 1718, p. 2.

[19] J. F. Gmelin: *Geschichte der Chemie seit dem Wiederaufleben der Wissenschaften bis an das Ende des 18. Jahrhunderts, vol. 1*, Rosenbusch, Göttingen 1797, p. 2: "der Abgott, vor welchem alle Völker und alle Stände, Fürsten und Unterthanen, geistliche und weltliche, Gelehrte und Ungelehrte, Hohe und Niedere die Kniee beugen; die Lieblingswissenschaft der Grosen, von deren glücklichen Ausübung sie sich goldene Berge, schleunige Wiederherstellung zerrütteter Finanzen, so wie zerrütteter Gesundheit, versprachen, ... die Zuflucht des Weisen, der Licht und Belehrung sucht; die wichtigste Hülfswissenschaft des Naturforschers, die ihm Aufschlus gibt, wo ihn andere Kenntnisse verlassen; der Schlüssel zu manchen Geheimnissen der Natur; der auserwählte Leitstern im Labyrinth zahlloser Gewerbe, die Menschen und Staaten ernähren, beglüken, bereichern, die vernünftige Grundlage des Hüttenwesens, vieler Fabriken, Künste und Handwerke ..."

Liquid Crystals: A Tool for Studies on Chirality

By Guy Solladié* and Richard G. Zimmermann

Nematic liquid crystals are extremely sensitive to optically active molecules, which, at very low concentration, convert them into cholesteric liquid crystals. The purpose of this report is to review recent applications of liquid crystals to chirality studies. A brief discussion of the structure and properties of liquid crystals is followed by a survey of the methods currently being employed for the determination of the pitch and handedness of cholesteric liquid crystals. Of special interest in the formation of induced-cholesteric phases are the twisting powers of optically active compounds and the structural relationships between dopants and nematics. Liquid crystals can be used, inter alia, for the detection of small optical activities and for the determination of thermal racemization barriers and absolute configurations.

1. Introduction

In 1888, while working with cholesteryl benzoate, the Austrian botanist *Reinitzer*[1] discovered a novel state of matter which was later to be termed cholesteric liquid crystal. Actually, *Reinitzer* gave a detailed description of the "two melting points" of this substance[2]. He found that the substance melts at 145.5 °C to give a cloudy but fully liquid melt, which at 178.5 °C suddenly becomes completely clear. On cooling the melt, he observed a violet-blue coloration which quickly disappeared, leaving the substance cloudy but still liquid. On further cooling, the violet-blue coloration reappeared and immediately afterwards the substance solidified to a white crystalline mass. *Reinitzer* sent the specimen to *Lehmann* at Karlsruhe, who initiated a systematic study of this and related phenomena. *Lehmann* coined the term "liquid crystal" and wrote the first monograph on this new topic of interest[3a]. In 1922, *Friedel* published an outstanding paper on the same topic[4] and coined the terms "mesophase", "nematic", and "smectic" phase. The first fully synthetic "liquid crystal", *p*-azoxyanisole (4,4'-dimethoxyazoxybenzene) **2** was prepared by *Gattermann* et al.[3b]. *Vorländer*[3c] was probably the next, and, for a long time, the only person who studied this topic in the organic chemistry sector.

Although liquid crystals have been known for a century or more, it is only in the past 20 years that their unusual properties, especially the color changes that they can undergo, have found widespread application. Liquid crystals have become indispensable for the manufacture of many electrically controlled display devices. Thus, they are the essential material in numerical displays on wrist-watches, pocket calculators, thermometers, and many other electrical and electronic devices. They are also of importance in the development of flat television screens, displays for portable instruments incorporating microprocessors, and in the manufacture of fibers (using macromolecular liquid crystals).

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For chemists and physicists studying the theory of matter, liquid crystals are of great interest because of their uniqueness, their not being true solids nor true liquids. However, in this review we will only be concerned with the application of liquid crystals to studies on chirality, a topic which has not been dealt with in detail in monographs[5] or reviews[6] on liquid crystals.

The liquid crystalline or mesomorphic state is intermediate between that of the solid and the liquid state, the associated order being less than that in solids but more than that in liquids. Although liquid crystals exhibit certain aspects of both the solid and liquid states, they also possess properties that are not found in either liquids or solids. Their ordering properties, for example, can be controlled by ordinary magnetic and/or electric fields. In some liquid crystals the optical activity is of an order of magnitude not met with in any solid, liquid or gas. Some liquid crystals change color as a result of the sensitivity of their structure to temperature. These are the properties on which the practical applications of liquid crystals are based. Basically, there are three types of liquid crystals (Fig. 1). Following a proposal by *Friedel*[4], they are designated as smectic, nematic, and cholesteric. Smectic phases have a two-dimensional structure characterized by the packing of molecules in strata or layers. The arrangement of the molecules within the layers may be either random or ordered, in either case the long axes of the molecules in a given layer are parallel to one another. There is a multiplicity of smectic modifications which correspond to various tilted or twisted arrangements of the molecules, including one which has a three-dimensional lattice structure. The physical appearance of the smectic state is that of a highly viscous, turbid fluid.

In the nematic phase the molecules are still oriented in a parallel fashion; however, the layer arrangement no longer exists. The resulting one-dimensional order is therefore less than that in the smectic phase. The nematic phase is turbid but much less viscous than the smectic phase.

The cholesteric phase occurs only in optically active compounds; it corresponds to a twisted nematic, i.e. it has a helical structure. In cholesteric phases there is a local nematic packing of the molecules. The director, however, is

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not fixed; it rotates spatially about an axis perpendicular to itself, conferring a helical structure on the system (Fig. 2).

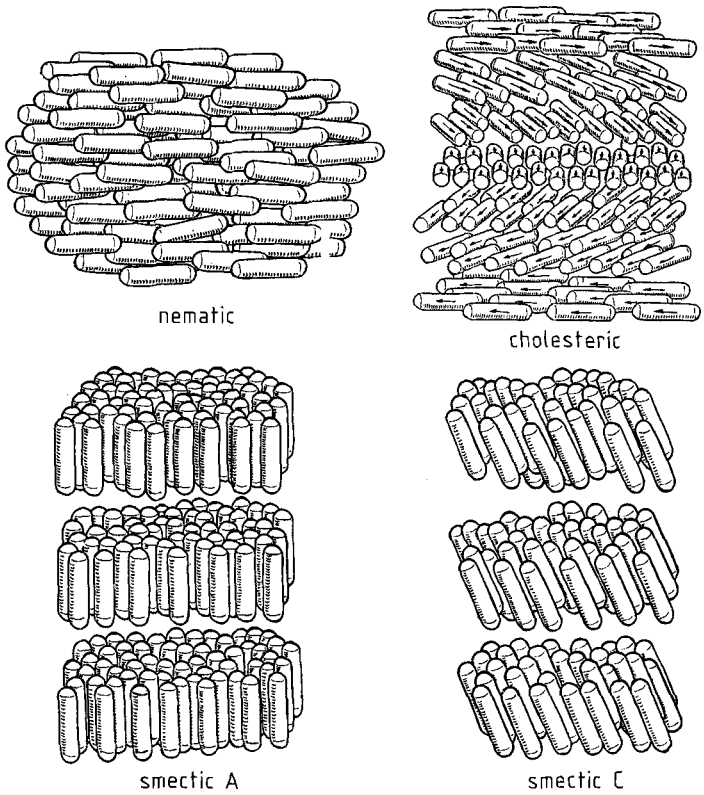


Fig. 1. Arrangement of molecules in thermotropic liquid crystals (see also Table 1).

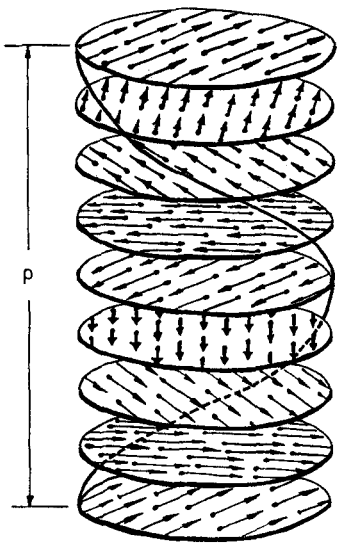


Fig. 2. The cholesteric helical structure. p is the pitch of the helix. The arrows indicate the long axes (or directors of the molecules). The figure shows a left-handed helix (M-helix).

The pitch p of the helix—the thickness corresponding to a 360° rotation of the director of the molecules—is typically of the order of 0.2—2.0 μm. Twisted smectic phases can also be obtained from optically active molecules. The characteristic iridescent color of the cholesteric phase results from the selective reflection of one circularly polarized component of light, as explained by the *De Vries* theory[22]. The behavior of incident light that is plane polarized will change as its wavelength increases. For wavelengths much shorter than the pitch of the helix, the combined wave remains linearly polarized but the direction of polarization is rotated by the spatial rotation of the helix. The molar rotatory power is extremely high; it can exceed 50000. As the wavelength is increased to a value nearly equal to the pitch, the clockwise circularly polarized light is increasingly reflected in the case of a right-handed cholesteric, the reflectivity reaching 100% when the wavelength is about equal to the pitch. In this region, the transmitted wave for a right-handed cholesteric is then solely anticlockwise circularly polarized. Since the width of this region with 100% reflectivity is quite narrow the reflected color appears very pure. For wavelengths longer than the pitch, the reflectivity decreases. Similar color effects seen

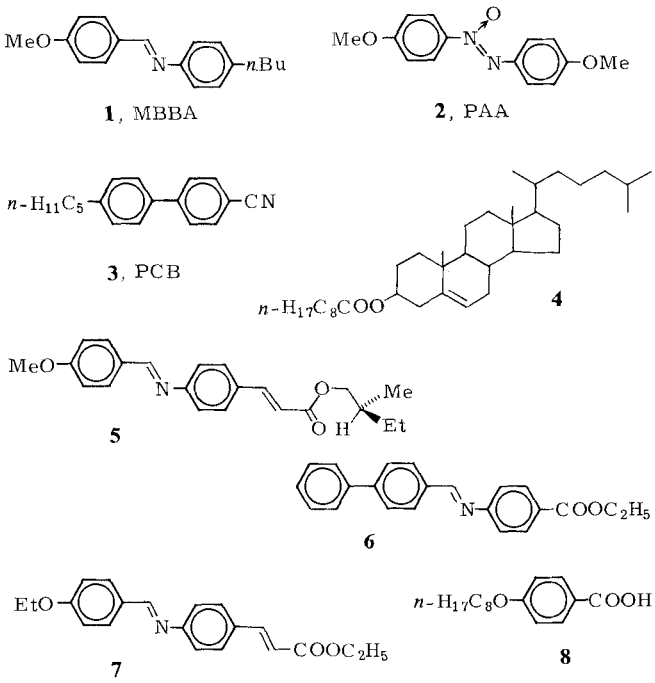


Table 1. Examples of thermotropic liquid crystals [5 h, 7] (cf. Fig. 1).

Compound	Liquid crystalline range [°C]	Liquid crystalline phase [a]
1 4-Butyl-*N*-(4-methoxybenzylidene)aniline (4-Methoxybenzylidene-4′-butylaniline, MBBA)	21–47	nematic
2 4,4′-Dimethoxyazoxybenzene (*p*-Azoxyanisole, PAA)	118.2–135.3	nematic
3 4′-Pentyl-4-biphenylcarbonitrile (4-Pentyl-4′-cyanobiphenyl, PCB)	22.5–35.5	nematic
4 Cholesteryl nonanoate	147–179	cholesteric
5 (−)-(2-Methylbutyl) 4-(4-methoxybenzylideneamino)cinnamate	76–125	cholesteric
6 Ethyl 4-(4-biphenylmethyleneamino)-benzoate	121–131	smectic A
7 Ethyl 4-(4-ethoxybenzylideneamino)cinnamate	77–116	smectic B
8 4-Octylbenzoic acid	108–147	smectic C

[a] Smectic A, B, and C: long axes of the molecules orthogonal (A, B) and tilted (C) to the layer planes, random arrangement (A, C) and hexagonal arrangement (B) within the layers.

in nature, on some beetles wings for instance, are due to the same phenomenon. Temperature, pressure, electric fields, magnetic fields, traces of impurities, and other effects influence the pitch of the helix and thus lead to different changes in color[5e]. Some examples of thermotropic liquid crystals are listed in Table 1.

The identification of mesophases, i.e. the phases of liquid crystals, involves observation of the melting process under a polarizing microscope and the identification of the various birefringent textures that are associated with the respective mesophases[5b]. The simplest texture is one in which the whole liquid crystal appears optically uniform. Nematics can be aligned in parallel by treating the microscope slide with polyvinyl alcohol[5g] or an organosilane[5f] and rubbing in one direction. The molecules tend to align themselves with their long axes in the direction they are rubbed. Helices in cholesteric phases can, in this way, be uniformly aligned with their axes perpendicular to the surface of the slide (planar texture). The color of this structure is caused by Bragg-like reflections associated with the periodicity of the cholesteric helix and can be observed without polarizers. Treatment of the slide with a surfactant such as *N*-cetyltrimethylammonium bromide, on the other hand, will cause perpendicular alignment of the molecules. Nematic liquid crystals not uniformly aligned will appear turbid.

A further method resorted to for the identification of such phases is that of differential thermal analysis, by means of which transition temperatures and specific heats can be determined.

2. Cholesteric Liquid Crystals: Pitch and Handedness

To fully characterize a cholesteric liquid crystal, the pitch and handedness of the helix have to be determined.

In 1922, *Friedel*[4] identified the cholesteric handedness from the sign of the reflected circularly polarized light—a difficult measurement with cholesterics having a large pitch. Later, in 1966, *Fergason*[8], using the helical model for cholesterics proposed by *Oseen*[10] and *De Vries*[22] from the experimental observations of *Mathieu*[9], established that a cholesteric liquid crystal, characterized by the helix pitch p, can reflect light of wavelength λ_0 directly proportional to the pitch:

$$\lambda_0 = \bar{n} \cdot p$$

where $\bar{n}$ is the mean refractive index. This equation holds if a parallel light beam propagating parallel to the helix axis is used for the measurement. The latter condition is easily fulfilled with a cholesteric phase displaying the planar texture (helix axis perpendicular to the object slide). Several papers[11-14] reported pitch determinations by this method, i.e. measurement of the reflection wavelength.

Baessler and *Labes*[15] proposed measurement of the transmitted light instead of the reflected light. This variant is especially valuable in the infrared region for large-pitch cholesterics (0.5 to 5 μm), where reflectance measurements are difficult.

Chiroptical techniques have also been used for pitch determinations. For small-pitch cholesterics, *Stegemeyer* et al.[16-20] determined the reflection wavelength by following the change in optical rotation with wavelength (optical rotatory dispersion, ORD) according to the theoretical predictions of *de Vries*[22].

For induced cholesterics, with pitches of about 10^{-1} to 10^{-2} μm, *Schrader* et al.[23,24] proposed that the infrared rotatory dispersion (IRD) should be investigated, because the reflection band in these cases lies in the infrared region: a positive reflection Cotton effect indicates a left-handed helical structure and vice versa.

Finally *Saeva* et al.[25-27] found that achiral molecules (such as MBBA **1**, naphthalene, or pyrene) dissolved in a cholesteric phase could display induced circular dichroism (ICD) corresponding to their own absorption bands, independently of the CD corresponding to the pitch band (reflection band) of the cholesteric. However, the sign of the liquid crystal-induced circular dichroism (LCICD) was observed to be dependent on the position of the cholesteric pitch band (λ_0) relative to the wavelength of absorption[27]. For induced cholesterics having the pitch band in the infrared, the signs of ICD and pitch CD are always opposite, but are both dependent on the handedness of the helix: a positive ICD band corresponds to a right-handed helix.

For all these spectroscopic measurements, the liquid crystal must be oriented in a planar alignment (axis of helix perpendicular to the slide) and thermostated cells must be used because of the extreme sensitivity of the pitch to temperature.

The other techniques used for determining the pitch and handedness of cholesteric phases involve observations with a polarizing microscope. They are, on the whole simple techniques and require the use of only very small amounts of material.

Some of these methods are variants of the Grandjean-Cano method[28,29], which is based on the observation of the disclination lines occurring in a wedge-shaped cholesteric sample under homogeneous planar boundary conditions. A very simple cell for this determination was recently described by *Berthault, Billard,* and *Jacques*[30]. When a thin layer of a cholesteric liquid crystal oriented in a planar alignment (helical axis perpendicular to the slide) in a cell of variable thickness is observed with a polarizing microscope, dark lines (the Grandjean-Cano steps) and bight lines appear which follow the lines of equal thickness. The distance between two consecutive Grandjean-Cano steps is equal to half of the pitch. If on using monochromatic plane polarized light (wavelength higher than the reflection wavelength) and on rotating the analyzer clockwise the extinction zone is displayed towards the large-thickness area, the helix is right-handed. This method was also recently described by *Gerber*[30c].

Heppke and *Oestreicher*[31,32] modified the method by using a spherical lens of the cholesteric liquid crystal on a glass slide. The spherical lens is first treated to provide a concentric planar surface alignment. Under such conditions the Grandjean-Cano (disclination) lines are spiral, and the sense of the helix screw can immediately be obtained from their handedness. The magnitude of the pitch

is obtained, as in the conventional Cano method, from the radial distance between two consecutive lines[33].

The droplet method[33] is also a very simple technique for determining the pitch. An emulsion of a small amount of a cholesteric liquid crystal in a solvent such as glycerol is prepared and the droplets of the cholesteric phase floating in the isotropic solvent are then observed under the microscope with polarized light. A spiral shaped optical pattern with a radial disclination is observed in each droplet (Fig. 3). The spiral shape is due to the boundary conditions at the surface of the droplet[34]. The optical pattern is actually either a spiral or a series of concentric rings, depending on whether the radial disclination lies in the direction of observation or in a plane perpendicular to it. Usually, both patterns are observed. It was **shown**[33] that the distance between two spirals is equal to half the pitch.

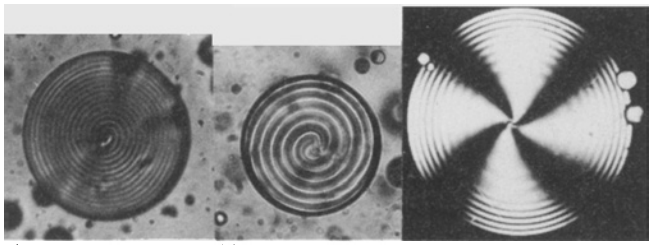


Fig. 3. The droplet method. Droplets of a solution of the diazocine **21** in the liquid crystal Licristal Merck IX. The droplets form an emulsion with glycerol and are observed under crossed nicols. a) Optically pure **21**, b) partially racemized **21**, c) racemic **21**. Licristal Merck IX consists of a mixture of aromatic esters.

Determination of the handedness of the helix by the droplet **method**[35] is based on the finding that a mixture of two cholesterics of opposite handedness and equal pitch gives a compensated nematic and that a nematic droplet displays a characteristic optical pattern[33]: with crossed nicols, a series of concentric rings and an extinction cross are observed, the latter of which rotates when rotating the polarizer and analyzer together (Fig. 3). This cross corresponds to the points on the surface of the droplet where the optical axis is parallel to either the analyzer or the polarizer. However, two reference cholesterics of opposite handedness are needed for this determination[35].

Another way of determining the pitch handedness is by the contact method, which is also based on a comparison with cholesteric phases of known helical sense[36–38]. When the interface of two cholesterics having the same helical sense is observed microscopically, no discontinuity in the texture is visible, i.e. a continuous cholesteric texture is observed from left to right across the field of view. However, when the helical twists are of opposite sense, a narrow band of nematic texture separating two cholesteric regions is observed.

Finally, magnetic resonance techniques can be applied to liquid crystals[39]. As *Gottarelli, Pedulli,* and *Zannoni*[40] have recently shown, EPR spectroscopy enables a rapid and reliable determination of both the pitch and the handedness of induced cholesteric mesophases. The spin probe used was 2,2,6,6-tetramethyl-4-piperidone *N*-oxide.

3. Twisted Nematic Phases: Induction of Cholesteric Phases by Addition of Chiral Compounds to Nematic Phases

More than 60 years ago, *Friedel*[4] described the close relationship between nematic and cholesteric liquid crystals: a small amount of a chiral compound, cholesteryl benzoate, dissolved in a nematic phase induces a cholesteric. The next paper on this topic appeared almost 50 years later, in 1969. *Buckingham* et al.[41] pointed out that a continuous change of a nematic phase to a cholesteric mesophase may be achieved by adding small amounts of optically active molecules, such as D-tartaric acid, which do not in themselves form a mesophase.

Following publication of *Buckingham*'s paper, numerous articles on induced cholesterics appeared in the literature. Two different approaches were developed simultaneously: *Baessler* and *Labes*[42] employed chiral compounds which themselves form cholesteric liquid crystals, while *Stegemeyer* et al.[16] directed their attention to chiral compounds which in themselves do not form liquid crystals.

In 1971, *Goosens*[21] published a molecular statistical theory of the cholesteric phase and of the twisting power of optically active molecules in a nematic liquid crystal. This theory of cholesteric liquid crystals is still of considerable importance (cf. [20d, 48]).

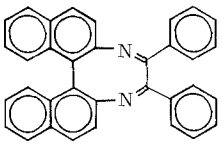
Baessler and *Labes*[42] used a compensated nematic liquid crystal, i.e. a mixture of two cholesteric liquid crystals of opposite handedness (cholesteryl chloride (CC), a right-handed cholesteric, and cholesteryl myristate (CM), a left-handed cholesteric). The extreme sensitivity of the pitch to temperature allowed exact compensation[43, 44], i.e. a nematic phase to be obtained, by a small change in temperature.

Sackmann et al.[43] and *Baessler* and *Labes* et al.[44] were the first to study the helical twisting power β, i.e. the ability of chiral compounds to convert nematic liquid crystals into cholesteric phases, using as example several steroids in the nematic liquid crystal of CC and CM. They showed that the concentration of optically active solute is inversely proportional to the pitch of the helix. For a series of fatty acid esters of cholesterol, the twisting power decreases with decreasing number of carbon atoms in the acyl group. However the helix of the induced cholesteric changes rotational sense if the acyloxy group is replaced by Cl, Br or OH[45]. This finding shows that the *induced helical sense is not only dependent on the chirality of the molecule but, for the same absolute configuration, also on the nature of the substituents.* The first model to explain the mechanism of the twist was proposed by *Baessler, Laronge,* and *Labes*[44]; they considered the side chain at the 3β-position of the steroid ring to be the important factor at the origin of the twist. Similar results were obtained with alkylcholesteryl carbonates[46]. The helical twisting power rapidly reaches saturation with increasing chain length, in accord with the model attributing this twist to the effective length of the alkyl chain.

Nakagiri[47] investigated the pitch in mixtures of nematic and cholesteric material (4-(4-methoxybenzylideneamino)phenylacetate and cholesteryl propionate) as a function

of the concentration of the cholesteric material. He found that the pitch of the helix is inversely proportional to the molar fraction of the cholesteric material only at low concentration. This finding was confirmed for a wide variety of components by *Stegemeyer* et al.[20a] and by *Dekker* et al.[49]. The dependence of the helical twisting power on the molar fraction x of the optically active doping molecule in cholesteric liquid crystals can be considered as linear only at low concentrations.

We now come to the twisting powers of optically active compounds which do not form liquid crystals. The first report in this direction was that published by *Stegemeyer* et al.[16,19], who found that the nematic phase of MBBA **1** is converted into a cholesteric phase by (−)-menthol. He and his co-workers[17,18] also showed that a chiral compound without any asymmetric carbon atom, e.g. diazocine **9**, is also able to transform the nematic MBBA into a cholesteric phase. Both enantiomers of **9** gave cholesteric phases having opposite handedness; the observed pitch was much larger than that in (−)-menthol.



9, DDCO

After this paper, a more quantitative study of the twisting powers of optically active compounds was started by several groups in order to obtain more information about the factors controlling nematic twists. Induced cholesteric phases are characterized by the presence of chiral guest molecules in a nematic host phase. The mole fraction of the chiral component has to be small (< 10 mol-%) in order to get a linear variation of the helix pitch with the concentration. Under such conditions the helical twisting power β_M is defined as:

$$1/p = \beta_M \cdot c$$

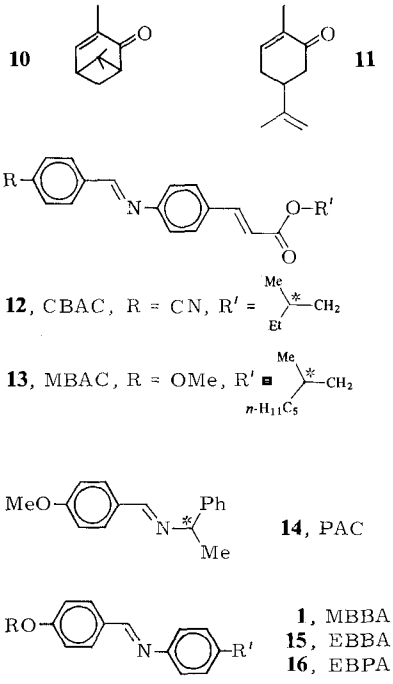
The helix pitch p is inversely proportional to the molar concentration c of the solute.

At such low concentrations the chiral molecules are isolated in a matrix of non-chiral nematic molecules. Consequently the helical structure will be induced only by interaction of the chiral molecules with the solvent molecules.

Finkelmann and *Stegemeyer*[20c] studied the helical twisting power as a function of the "chiral character" of the guest molecules. They determined pitches p by the Grandjean-Cano method and β_M from the slopes of the plots $1/p$ vs molar fraction x (in mol-%). The results are listed in Table 2.

From the data given in Table 2 it can be concluded that:

- The strongest twist is induced by the inherently dissymmetric molecule **9** (DDCO) (pitch $p = 1.5$ μm, $x = 0.02$), the weakest by verbenone **10** ($p = 132$ μm, $x = 0.065$).
- Cholesterol derivatives and chiral nematics show higher twisting powers than small molecules with asymmetric carbon atoms.



10 **11**

12, CBAC, R = CN, R′ = Me, Et, CH₂

13, MBAC, R = OMe, R′ = Me, n-$H_{11}C_5$, CH₂

14, PAC

1, MBBA, R = Me, R′ = nBu
15, EBBA, R = Et, R′ = nBu
16, EBPA, R = Et, R′ = n-C_5H_{11}

Table 2. Twisting powers β_M of chiral compounds [20c]. The table gives no information about the helical sense.

Chiral compound	Nematic phase	β_M [μm^{-1}·mol^{-1}]
10 (−)-Verbenone	**1** MBBA	0.1
L-(−)-Amyl alcohol	**1** MBBA	0.2
D-Amyl acetate	**1** MBBA	0.4
(+)-2-Octanol	**15** EBBA	0.5
	ZLI 304 [a]	0.5
	1 MBBA	0.8
D-Amyl benzoate	**1** MBBA	1.0
11 (−)-Carvone	**16** EBPA	1.6
	15 EBBA	1.9
(−)-Menthol	**1** MBBA	2.2
11 (−)-Carvone	**1** MBBA	2.3
12 CBAC	**16** EBPA	3.2
	15 EBBA	3.3
	1 MBBA	3.5
Cholesteryl chloride (CC)	**1** MBBA	9.3
Cholesteryl propionate (CP)	**16** EBPA	12.2
Cholesteryl [2-(2-ethoxyethoxy)-ethyl]carbonate (CEEC)	**15** EBBA	12.4
Cholesteryl propionate (CP)	**15** EBBA	13.5
	1 MBBA	15
α-Phenylethylamine (PEA)	**1** MBBA	15.3
14 PAC	**1** MBBA	17.1
13 MBAC	ZLI 304 [a]	17.8
	1 MBBA	19.4
9 DDCO	**1** MBBA	32

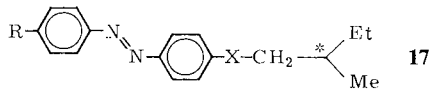
[a] Mixture of azoxybenzenes (Merck).

- The surprisingly high twisting power of α-phenylethylamine is probably due to amine-exchange reactions with the Schiff-base-type nematic **1**[50], a result consistent with the β_M value of **14** in **1**.
- Helical structures of cholesteric systems built up by esters of cholesterol are much more twisted than can be achieved by chiral molecule-host interactions (pitch $p \approx 0.2$ μm).
- The influence of nematic host phases on the induction of the helical structure is rather small and increases

along the series EBPA < EBBA < MBBA. However, these host phases are quite similar.

The "chirality character" of the guest molecule is not simply related to its optical rotation. **9** (DDCO) has undoubtedly the highest rotation ($[\alpha]_D$ +2000) and also the highest twisting power, but the β_M value of carvone **11** exceeds that of verbenone **10** by a factor of 20, while the optical rotation of verbenone ($[\alpha]_D$ +237) is higher than that of carvone ($[\alpha]_D$ +62.2). Geometrical factors probably also play a role.

Nematic azobenzene derivatives of type **17** with asymmetric side chains have been systematically investigated[51] in order to establish the influence of the structure on the pitch and handedness of the helix. Some of the results are listed in Table 3.



17

Table 3 [51]. Pitch p, twisting power β (helical sense of mixtures of 20 wt.-% chiral azobenzene derivative **17** and 80 wt.-% nematic liquid crystal Merck N5. This liquid crystal consists of a eutectic mixture of azoxy compounds.

R	X	p [µm]	β [a]
OMe	—	+0.45	+11.1
OEt	—	+0.46	+10.9
O-*n*Pr	—	+0.48	+10.2
O-*n*Bu	—	+0.52	+ 9.6
O-*n*-C_5H_{11}	—	+0.59	+ 8.5
O-*N*-C_6H_{13}	—	+0.62	+ 8.1
O-*n*-C_8H_{17}	—	+0.61	+ 8.2
OCH_2–*CHMeEt	—	+0.65	+ 7.7
OCH_2–*CHMeEt	–O–	−1.06	− 4.7
CH_2–*CHMeEt	—	+0.28	+ 7.9
OEt	$-CH_2-$	−0.57	− 8.8

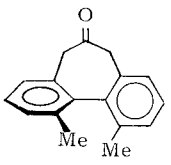
[a] The twisting powers $\beta = 1/(0.2p)$ relate to concentrations in g/100 g and not in mol/L. A positive sign refers to a right-handed helix and vice versa. The pitches were determined by the Grandjean-Cano method and the helical sense from the sign of the optical rotation in the visible region.

Noteworthy in Table 3 is that:

In the upper part of the table, the pitches increase gradually with the chain length, as observed with cholesteryl esters[42,45,46] in compensated nematic and in optically active naphthoxyalkanoic acids in tolans and aromatic esters[30].

In the lower part of the table, the handedness of the helix changes when a 2-methylbutyl side chain is replaced by a 2-methylbutoxy side chain or both side chains are replaced by an ethoxy and a 3-methylpentyl side chain. This implies that the helical sense depends on the number of atoms in the side chain and not only on the chirality, a fact which has been confirmed by *Gray* et al.[38] with non-steroid cholesteric liquid crystals.

We have investigated more closely the influence of the structure of nematic liquid crystals on the twisting power of optically active compounds[52]. The pitches were determined by the droplet method. Table 4 lists the twisting powers of the optically active ketone **18** in several nematic phases. The results suggest that there is a close relationship between the host compound and the optically active guest compound. *Twisting powers are higher when the chiral molecule has a structure similar to the nematic:* A chiral bridged biphenyl such as **18** has a stronger twisting power in a biphenyl-like nematic phase such as PCB. As follows from Table 2, molecules having only one asymmetric carbon atom show high β_M values when they exhibit a close structural similarity with MBBA **1**; this is true for PAC **14**, MBAC **13**, and α-phenylethylamine (after amine-exchange reaction with the solvent).



18

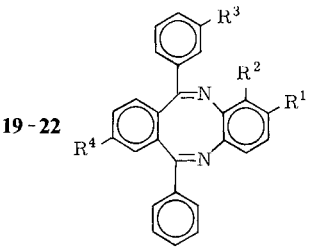
Table 4. Twisting powers β of 4,5-dimethyl-9,11-dihydrodibenzo[*a*,*c*]cycloheptan-10-one **18** in nematic liquid crystals [52]. **18**: $[\alpha]_D^{20}$ +617. MBAB: 4-butyl-4′-methoxyazoxybenzene; tolans: 52.5% 1-(4-methoxyphenylalkynyl)-4-pentylbenzene and 47.5% 1-(4-heptylphenylalkynyl)-4-propoxybenzene.

	Nematic phase			
	MBAB	MBBA **1**	Tolans	PCB **3**
β [a]	9.3	10.2	10.4	15.2
β_M [b]		8.8		13.5

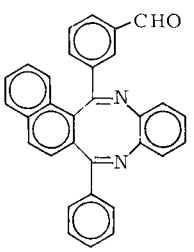
[a] [µm^{-1}]. [b] [µm^{-1}].

We also investigated the twisting powers of the optically active diazocines **19** to **23** in MBBA **1**[53]. Table 5 lists the results, including our values for (−)-menthol and cholesteryl propionate (CP), which are in good agreement with the values reported by *Stegemeyer* et al.[20c] (Table 2).

Table 5 shows that diazocines have very strong twisting powers in MBBA and that the location of the aldehyde



19-22



23

Table 5. Twisting powers β of the diazocines **19-23** and some reference compounds in MBBA **1** [53]. CP = cholesteryl propionate. The table gives no information about the helical sense.

Chiral compound	R^1	R^2	R^3	R^4	$[\alpha]_D$	β [a]	β_M [b]
(−)-Menthol						3	1.7
18					+617	10.2	8.8 [c]
CP						8.4	13.9
19	H	H	H	CHO	− 33	11	15.9
20	H	CHO	H	H	+242	12	17.3
21	CHO	H	H	H	+277	16	23.1
9							32 [49]
22	H	H	CHO	H	− 43	30	43.4 [d]
23					+154	27	44

[a] [µm^{-1}] (wt-%). [b] [µm^{-1}] (mol-%). [c] β_M in PCB **3**: 13.5. [d] β_M in PCB **3**: 23.2.

function, which is at the origin of the molecular dissymmetry, is very important: R^3 appears to have the greatest influence. In addition, it is shown that the twisting power of diazocine **22** in PBC **3** is only half that in MBBA **1**, whereas with the biphenyl ketone **18** the opposite is the case.

These findings emphasize once again that a close structural analogy between the chiral guest and the nematic host is necessary to achieve a large twist, probably because of a better intermolecular arrangement and therefore a better chirality transfer. Figure 4 shows the structural similarity between diazocines and MBBA, which is due to the tub-like conformation of the eight-membered heterocycle.

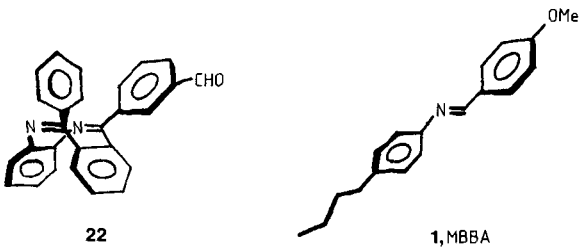


Fig. 4. Structural analogy between diazocines such as **22** and MBBA **1**.

The twisting powers of stereoidal molecules are also strongly dependent on the structure of the nematic host[54].

If we compare our results with those obtained in a compensated nematic phase (mixture of cholesteryl chloride and cholesteryl myristate)[42,45,46], it is evident that cholesterol esters in PCB **3** do not show any significant variation in β_M values with the chain length ($\beta_M = -9.1$ to -9.7 μm^{-1} (mol-%)$^{-1}$, but certainly do so in steroidal nematics ($\beta_M = +2$ to -7.5). These twisting powers are even higher in other nematics[35]: for cholesteryl myristate, $\beta_M = -25.2$ in MBBA **1** and -16.7 in MBAB (4-butyl-4′-methoxyazoxybenzene).

Finally, substituted cholestadienes **24** with various aryl groups on C-3 showed an interesting change in helix handedness in aromatic nematic phases[54] (Table 6).

While all the cholesterol esters displayed left-handed helices in these aromatic nematic phases, we observed right-handed twists with 3-arylcholestadienes when there was no *o*-substituent on the aromatic ring. Therefore the coplanarity of the aromatic ring and the double bonds in the steroid moiety, in other words the *conformation of the molecule, also appears to be an important factor.*

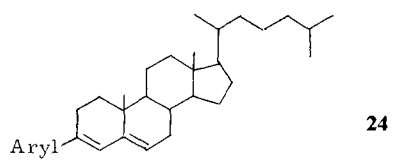


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Table 6. Twisting powers β_M of 3-arylcholestadienes **24** in aromatic nematic phases [54]. MBAB = 4-butyl-4′-methoxyazoxybenzene.

Aryl	β_M [μm^{-1} mol^{-1}]		
	PCB **3**	MBBA **1**	MBAB
2-Me–C_6H_4	−3.2	− 1.7	−2.7
4-Me–C_6H_4	+6.8	+12	+5.1
4-MeO–C_6H_4	+8.1	+15.6	+2.7
4-Ph–C_6H_4	+8.2	+ 7	+3.1

In summary it emerges that:

- A small amount of an optically active molecule will twist any nematic liquid crystal to a cholesteric phase.
- Two enantiomers will twist a nematic phase to cholesterics of opposite handedness.
- The resulting pitch is inversely proportional to the concentration of the optically active compound and to its optical purity (at least at low concentrations).
- The magnitude and sign of the twisting power of an optically active molecule in a nematic result from solute-solvent interactions.

Therefore, aside from geometrical factors, structural analogies between solute and solvent, and conformational factors, the type of chirality involved is very important. As shown by *Jacques* et al.[30b,55], globular molecules such as camphor and verbenone or small molecules having only one asymmetric carbon atom[49,56,57] will generally show very low twisting powers. However, derivatives of such compounds having a similar structure to the nematic will display higher twisting powers[56]. Inherently asymmetric or dissymmetric molecules, such as biphenyl and diazocine derivatives, will show high twisting powers if a suitable nematic is used and if geometrical factors are compatible (β-values of spiro compounds were found to be very low[58]). The sense of twist does not only depend on the absolute configuration of the molecule. In a given series of molecules having the same chirality, the handedness of the twist can be modified by geometrical factors, by conformational factors, or by using another type of nematic phase.

4. Applications of Liquid Crystals to Studies on Chirality

The extreme sensitivity of nematic liquid crystals to optically active compounds enabled stereochemical information to be obtained by generation of induced-cholesteric liquid crystals.

4.1. Detection of Very Small Optical Activities

A cholesteric liquid crystal is characterized by a very high macrostructural chirality. Therefore optical activity which is not detectable by polarimetric methods, owing to the small quantity of material available and/or very low rotatory power, can be amplified by the phenomenon of induction of a cholesteric mesophase. The induced-cholesteric can then be easily identified even in the case of large pitch by the Grandjean-Cano method, by the droplet method, by IRD (infrared dispersion), or even by measuring the rotatory power on a microscope[59].

This approach was already used in 1968 by *Jacques* et al.[55] to follow spontaneous resolution of conglomerates.

Korte[60a] showed that induced cholesteric could be used to detect the optical activity of 3 μg of tyrosine methyl es-

ter by IRD. He also showed that 70 μg of optically active cyclophosphamide, an anticancer drug, could easily be detected by IRD of a solution in 4-butyl-4′-methoxyazoxybenzene. This finding made the study of the metabolism of cyclophosphamide easier. A polarimetric study would have necessitated a total 24h sample of urine from the patient, which is about 100 times more than that required by the liquid crystal technique. A similar method was recently proposed by *Gottarelli* et al.[60b] for the determination of traces of heroin.

Gottarelli et al.[61] used induced cholesterics to characterize chiral compounds obtained by deuterium substitution. Such species generally exhibit a very low optical rotation. The twisting powers of these chiral deuterated compounds were small (Table 7)—about two orders of magnitude smaller than those observed with chiral secondary alcohols—but pitch and handedness in the helices of the corresponding induced-cholesterics could be determined by the Grandjean-Cano method.

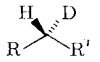
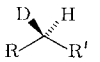
25   *ent*-**25**

Table 7. Twisting powers β_M of chiral deuterated compounds of type **25** and *ent*-**25** in a 1:1 mixture of MBBA **1** and EBBA **15**.

R	R′	β_M [μm^{-1} mol^{-1}]	
		25	*ent*-**25**
Ph	$OCOC_6H_4NO_2$-*p*	+0.093	−0.096
$PhCH_2CH_2$	OH	+0.079	−0.075
Ph	$CH_2NMeCOPh$	−0.113	+0.109

Both enantiomers always gave β_M values of opposite sign. The twist handedness changes, in spite of the same absolute configuration.—The method requires only two drops of liquid crystal and a very small amount of chiral compound.

4.2. Determination of Thermal Racemization Barriers

The pitch of induced cholesterics is inversely proportional to the concentration of the optically active solute and its enantiomeric purity r[71]:

$$1/p = \beta_M r c$$

Consequently, it should be possible to follow the kinetics[62a] of thermal racemization of optically active compounds by merely measuring the variation in pitch of a cholesteric mesophase, prepared by doping a nematic with the thermally racemizing optically pure compound, as a function of time. The higher the twisting power of the solute, the smaller the quantity of material necessary for the study. The host phases must be nematic at room temperature and stable at the racemization temperature, since the racemization occurs in the isotropic phases.

We first studied the racemization of diazocine **21** brought about by inversion of the eight-membered heterocycle[62b]. The pitch, as determined by the droplet method, typically varies during the racemization between 5 μm and 50 μm. The nematic used was a mixture of aromatic esters (Licristal Merck IX, nematic between −20 and +60 °C). The racemization, a first-order reaction, follows the relation

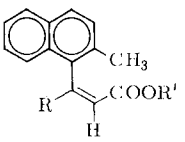
$$\ln(1/p) = -2kt + \ln(1/p_0)$$

where p_0 is the pitch in the starting material. The free enthalpy of activation for the racemization $\Delta G^{\neq}$ is 39 ± 1 kcal/mol at 188 °C, a value consistent with the barrier determined by NMR spectroscopy[63].

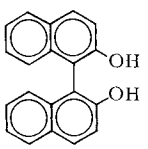
This method of determining thermal racemization barriers has two main advantages:

- Only extremely small quantities of optically active material are needed (less than 10 mg).
- The determination of rate constants from pitch variations is very accurate. The pitches are determined by the droplet method. It is not necessary to weigh exact quantities of material (the main source of error in the polarimetric method).

Recent results which we obtained on optically active atropisomers are collected in Table 8. They illustrate the wide range of temperature which can be used.



26, R = Cl, R′ = H
27, R = R′ = Me



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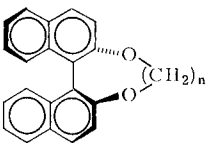


29, n = 1
30, n = 3
31, n = 4

Table 8. Racemization barriers of atropisomers from pitch changes in liquid crystals.

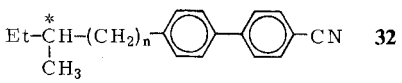
Cpd.	Nematic phase	T_{rac} [°C]	k_{rac} ($\times 10^{-6}$)	$\Delta G^{\neq}$ [kcal/mol]	Ref.
26	MBAB [a]	80	21	28	[64, 65]
27	PCB **3**	103	12	30.5	[65]
		132	185		[67]
28	1052 [b]	201	46	37.5	[68]
29	1052 [b]	181	787	33.4	[65]
		158.5	125	33.2	[68]
30	1052 [b]	298	3580	40.5	[68]
		264.5	99	41.9	[68]
31	1052 [b]	298	132	44.2	[68]
		264.5	15	43.9	[68]

[a] 4-Butyl-4′-methoxyazoxybenzene (Licristal Merck IV). [b] Nematic phase Merck 1052, binary eutectic of aromatic esters.

4.3. Determination of the Absolute Configurations

Addition of enantiomers to nematic liquid crystals produces cholesteric phases of opposite handedness. It has been known for some time[42] that cholesterol esters give left-handed, while cholesteryl chloride gives right-handed

cholesterics. More recently *Gray* and *McDonnell*[38] reported that in the case of optically active biphenyl liquid crystals having one chiral center in the side chain, the helical handedness cannot be simply correlated with the absolute configuration of the chiral center. (*S*)-**32**, with an even number of carbon atoms between the asymmetric center and the benzene ring gave a right-handed helix, whereas with an odd number of carbon atoms, a left-handed helix was formed. (This is also the case when some of the CH_2-groups are replaced by oxygen atoms.) We also found[54] that opposite twist can be obtained from the same enantiomer in different nematics, probably through conformation effects due to the substituents.



32

Therefore, the use of liquid crystals for the determination of the absolute configuration of optically active solute from the handedness of the resulting cholesteric helix requires a far better knowledge of the mechanism of the twist of nematics by chiral molecules. *Saeva*[69] was actually the first to recognize this. He added the compounds (*S*)-**33**, (*S*)-**34**, (*R*)-**35**, and (*S*)-**36**, which contain one simple chiral center of known configuration, to the nematic mesophases MBBA **1** and BPC [butyl-[4-(4-ethoxyphenoxycarbonyl)phenyl] carbonate]. The chirality of the resulting cholesteric mesophase was determined by LCICD[25-27] (Table 9).

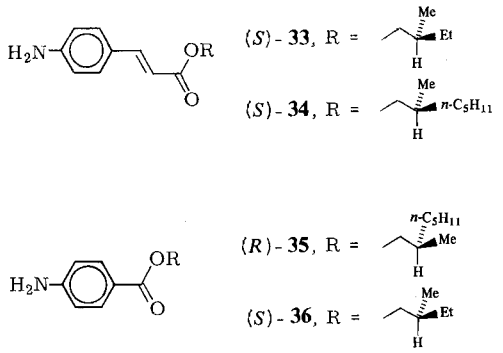


Table 9. Chirality of cholesteric mesophases produced from the nematic phases MBBA 1 or BCP and chiral compounds [69]. BCP is butyl [4-(4-ethoxyphenoxycarbonyl)phenyl] carbonate.

Chiral compound	Helical sense of the induced cholesteric phase
(*S*)-**33**	right-handed
(*S*)-**34**	left-handed
(*R*)-**35**	right-handed
(*S*)-**36**	right-handed

The 2-methylbutyl group in the aminocinnamate (*S*)-**33** and in the aminobenzoate (*S*)-**36** induces a right-handed helix, both in MBBA and in BPC. However, on going from (*S*)-2-methylbutyl to (*S*)-2-octyl aminocinnamate (*S*)-**34**, cholesteric mesophases of opposite handedness are produced. From these results, *Saeva* concluded that different diastereoisomeric interactions in the nematic-solute complex lead to an energy difference in the helical structures and, thus, to a preference of one helical sense over the other. Prediction of the helical sense of the induced cholesteric mesophases requires detailed energy calculations for the guest-host complex. However, enantiomers always appear to generate cholesteric mesophases with different helical sense.

For these reasons, many exceptions can be found to the correlation proposed by *Schrader* et al.[70-72]. These authors investigated over one hundred compounds having only one chirality center in an equimolecular mixture of MBBA **1**-EBBA **15** or in 4-butyl-4′-methoxyazoxybenzene (Licristal Merck IV). The induced cholesteric handedness was determined from the reflection Cotton effect in the IR region[24] (IRD). *Schrader* et al. proposed characterization of the absolute configuration of these chiral molecules by a sequence of ligand parameters in analogy to the Cahn-Ingold-Prelog nomenclature, but based on the "effective volumes" of the substituents of the asymmetric carbon atom, and to correlate this nomenclature to the sign of the Cotton effect observed in the IR region. Although this correlation is suitable for a larger number of molecules, it doesn't explain the observations of *Saeva*[69] (Table 9), some of the results of *Tsukamoto* et al.[51] (Table 3), the results obtained on compounds having several chiral centers, the dependence of the twist sense on the structure of the nematic phase, and the effect of the length of side chain observed by *Gray*[38].

As pointed out by *Gottarelli* et al.[73], the effective volume approach is an oversimplification which can at best only function within a single series of compounds or a favorable set of molecules. These authors studied numerous optically active sulfoxides. To explain the observed twist sense, the effective volume rule requires one to consider that the ethyl group is smaller than phenyl in 4-butyl-4′-methoxyazoxybenzene but larger in MBBA **1**. The benzyl group must also be considered as being smaller than all other groups, methyl included. The authors therefore concluded that the sequence of effective volumes does not agree with the observed twist sense, at least for a whole set of sulfoxides.

In order to obtain a correlation, additional experimental information about the specific interactions of the solute with the liquid crystal and the orientational properties of the solute is necessary. *Gottarelli* et al.[74] were the first to determine the twisting powers of a set of alcohols and amino alcohols of known absolute configuration in MBBA **1**; the chirality of the resulting cholesterics was determined by CD at the band edge of the MBBA absorption (the reflection band lay in the IR).

As shown in Table 10, for the aromatic compounds **37** to **45** there is indeed a correlation between the chirality of the induced helix and that of the inducing compound: for all the compounds having the same absolute configuration the sign of the CD band is the same. Even **41** and **42** fit in the scheme if the nitrogen atom is not taken into consideration; (*R*)-**41** and (*S*)-**42** would then be present. However, the correlation seems to be more complicated in the case of aliphatic molecules.

However, *Gottarelli, Samori,* and *Stremmenos*[75] obtained some additional information about the solute orien-

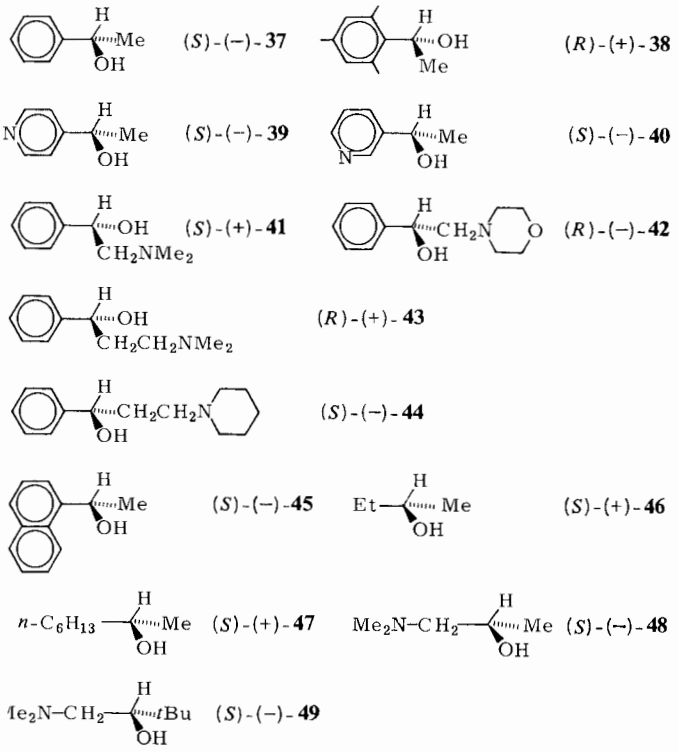


Table 10. CD-signs of cholesteric mesophases produced from MBBA **1** and chiral alcohols and amino alcohols [74].

Chiral compound	CD signs	Chiral compound	CD signs
(*S*)-(−)-**37**	(+)	(*S*)-(−)-**44**	(+)
(*R*)-(+)-**38**	(−)	(*S*)-(−)-**45**	(+)
(*S*)-(−)-**39**	(+)	(*S*)-(+)-**46**	(−)
(*S*)-(−)-**40**	(+)	(*S*)-(+)-**47**	(−)
(*S*)-(+)-**41**	(−)	(*S*)-(−)-**48**	(+)
(*R*)-(−)-**42**	(+)	(*S*)-(−)-**49**	(+)
(*R*)-(+)-**43**	(−)		

tation in the liquid crystal phase. From the IR spectra of α-phenylethanol in MBBA **1**, they demonstrated that the hydroxy group was hydrogen bonded to the nitrogen in MBBA—a result which is at the origin of a possible explanation of why (*S*)-(−)-α-phenylethanol induces a right-handed helix in MBBA. In the model by *Gottarelli* et al. (Fig. 5), the phenyl group of α-phenylethanol is in a preferred conformation and superimposed onto a phenyl ring of MBBA. The bulkiness of the methyl group, which in the two possible stackings of α-phenylethanol and MBBA lies farther from the centroid of the MBBA molecule and therefore causes less steric interactions with MBBA, prevents parallel covering of a second molecule of MBBA; thus a right-handed helix is formed with (*S*)-α-phenylethanol.

To form an ideal helix, one molecule of MBBA should interact with one molecule of alcohol. Therefore, at the very low concentrations used there must be a twisted area around the dopant molecules as well as undisturbed zones. Such a model is consistent with the inverse dependence of the pitch with concentration[76].

This model is valid for many aromatic alcohols or *N,N*-disubstituted amino alcohols[77], as shown in Table 11.

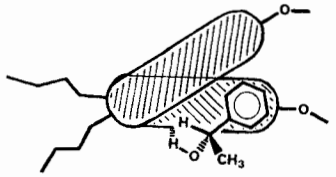


Fig. 5. Model for the interaction between (*S*)-α-phenylethanol and MBBA **1**. The central region of MBBA is represented by the dashed area. It forms a right-handed helix.

Only one exception has so far been reported: 2,2,2-trifluoro-1-phenylethanol. This compound has a very small twisting power, which (because of the presence of a phenyl group and a trifluoromethyl group on the asymmetric carbon atom) is probably due to competitive orientations of the solute in the nematic phase. When the phenyl ring is replaced by a naphthyl group, which will be much better aligned parallel to the nematic director, the twisting power is higher, and the twist sense is still in agreement with the model. The same effect was observed by *Pirkle* and *Rinaldi* with the 9-anthryl group[78]. However, these authors slightly modified the Gottarelli model to correlate the configuration of alcohols having a trifluoromethyl group in the absence of strongly orienting substituents such as naphthyl or anthryl. They proposed, in addition to the hydrogen bonding between the hydroxy group and the nitrogen lone-pair (an experimental fact), a bonding interaction of the α-hydrogen atom with one of the aromatic rings of MBBA. This double bonding interaction results in a conformation in which both the aryl and alkyl substituents are quasi-perpendicular to the long axis of MBBA. Such a conformation is certainly not favored in liquid crystals, the aromatic groups having the property to align in a liquid crystalline matrix with their long axes parallel to the nematic director[79].

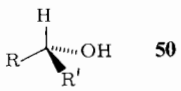


Table 11. Chirality of cholesteric mesophases produced from MBBA **1** and chiral arylmethanols **50** [77]. The helical sense of the induced cholesteric phase is given as "helicity" (*P* = right-handed, *M* = left-handed).

R	R′	Abs. config.	Induced helicity	β_M [μm^{-1} mol^{-1}]
Phenyl	CF_3	*S*	*P*	+0.2
	CH_3	*R*	*M*	−1.0
	Et	*R*	*M*	−1.3
	*i*Pr	*R*	*M*	−1.4
	*t*Bu	*R*	*M*	−1.5
1-Naphthyl	CH_3	*R*	*M*	−7.7
	CF_3	*S*	*M*	−8.5
2-Naphthyl	CF_3	*S*	*M*	−8.1

More recently, *Rinaldi* et al.[80] used MBBA **1** to correlate the absolute configurations of α-substituted benzylamines **51**. A number of years ago *Stegemeyer* et al.[20] and *Labes* et al.[50] pointed out that optically active α-phenylethylamine displayed very high twisting powers in MBBA because of a transamination reaction; hence, the sense of the induced helix in MBBA was brought about by interactions between MBBA and optically active Schiff-bases. *Ri-*

naldi et al. confirmed that synthetic Schiff bases **52** displayed a LCICD behavior in MBBA very similar to that observed with the corresponding amines **51** in MBBA. Therefore, the correlation of the absolute configurations (Table 12) must be described in terms of an interaction model very similar to the one proposed by *Gottarelli* for benzylic alcohols.

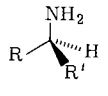
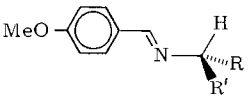
51   **52**

Table 12. Chirality of cholesteric mesophases produced from MBBA **1** and chiral α-substituted benzylamines **51** and Schiff bases **52** [80]. The liquid crystal induced circular dichroism (LCICD) was negative in all cases.

	R	R′		R	R′
51	Ph	Me	**51**	4-$O_2NC_6H_4$	Me
	Ph	Et		4-BrC_6H_4	Me
	Ph	*i*Pr		4-MeC_6H_4	Me
	Ph	*c*Hex		2-Thienyl	Me
	Ph	*t*Bu		2-Naphthyl	Me
	Ph	$PhCH_2$		1-Naphthyl	Me
				2,4,5-$Me_3C_6H_2$	Me
52	Ph	Me			
	Ph	Et			
	Ph	*t*Bu			

The Schiff bases **52** will align with their long axes parallel to the long axis of MBBA (Fig. 6). In (*S*)-**52**, the large R′ group leads to formation of a left-handed helix.

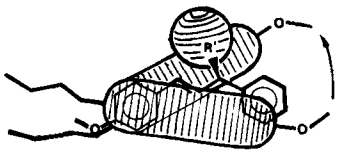


Fig. 6. Model for the interaction between chiral Schiff bases of type (*S*)-**52** and MBBA **1**. The central region of MBBA is represented by the dashed area. It forms a left-handed helix.

Recently, *Rinaldi*[81] extended these studies to β-amino alcohols **53**, which are also transaminated in MBBA. In addition, some hydrogen bonding between the hydroxy group and MBBA can contribute to the orientation of the solute in the solvent (Table 13).

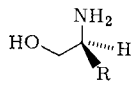
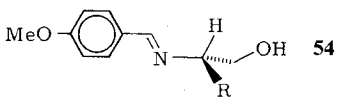
53   **54**

Table 13. Chirality of cholesteric mesophases produced from MBBA **1** and chiral β-amino alcohols **53** and Schiff bases **54** [81].

	R	LCICD		R	LCICD
53	Me	(−)	**53**	$MeSCH_2CH_2$	(+)
	Et	(+)		$EtSCH_2CH_2$	(+)
	*n*Pr	(+)		$PhCH_2SCH_2CH_2$	(+)
	*i*Pr	(+)		Ph	(+)
	*n*Bu	(+)		$PhCH_2$	(+)
	Me_2CHCH_2	(−)		4-$HOC_6H_4CH_2$	(+)
	EtMeCH	(+)		4-$MeOC_6H_4CH_2$	(+)
54	CH_3	(−)			
	Et	(+)			
	*i*Pr	(+)			
	Me_2CHCH_2	(−)			
	Ph	(+)			

Rinaldi et al.[81] proposed an interaction model of the type depicted in Figure 6 for these compounds. However, two exceptions to this model were found: the compounds in which R is a methyl and an isobutyl, respectively. Hence, the simple prerequisites of the model do not suffice to deal with the real situation. For example, in the preceeding discussion, the MBBA molecules were assumed to be planar, which in reality is not true. The *p*-substituted benzylideneaniline-type compounds such as MBBA **1** or EBBA **15** are known to be non-planar[82]; the angle between the planes of the two phenyl groups lies between 41 and 55°. Such a conformation is stabilized by electronic interactions between the nitrogen lone-pair and the π-electrons. Recent work on EBBA **15** in the crystalline[83] and in the liquid crystalline state[84] confirms this conformation.

At this point, in collaboration with Professors *Gottarelli* and *Samori*, we reached the following conclusions:

- Any future interacting model should take into consideration that MBBA has a skewed non-planar conformation.
- Such studies should be done only with molecules having high twisting powers (i.e. with good organization within the liquid crystal matrix).
- Experimental data about the solute orientation in the liquid crystal matrix should be obtained.

Optically active *trans*-stilbene oxides and analogous compounds were investigated[85], and it was shown that *trans*-diaryl molecules such as **55** have a much higher twisting power in MBBA than in any other liquid crystal (Table 14). This is a further example of the influence of structural and conformational similarity on the twisting powers. The results listed in Table 15 confirm this statement.

Information about the orientation of guest molecules in the liquid crystalline matrix were obtained by measurement of the linear dichroism (LD). The liquid crystalline matrix must be transparent in the UV/VIS region.

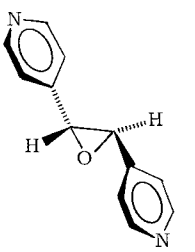
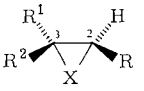
 (*R*,*R*)-**55**

Table 14. Twisting powers β_M of **55** in nematic liquid crystals [85].

Liquid crystals	Type	β_M [μm^{-1} mol^{-1}]
1 MBBA	Schiff base	−42
Phase IV	Azoxybenzene	−29
E_7 [a]	Biphenyl	−11
1083	Phenylcyclohexane	−10
ZLI 1167	Bicyclohexane	− 3

[a] Mixture of 4′-aryl- and 4′-*n*-alkyl-4-biphenylcarbonitrile.



55 - 66

Table 15. Twisting powers β_M of chiral oxiranes and thiiranes **55-66** in MBBA **1** [85].

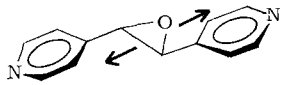
	R	R^1	R^2	X	Abs. config.	β_M [a]	Induced helicity
56	Ph	Ph	H	O	2*R*,3*R*	−35	*M*
55	4-Pyridyl	4-Pyridyl	H	O	2*R*,3*R*	−42	*M*
57	Ph	Ph	H	S	2*R*,3*R*	−26	*M*
58	Ph	Me	H	O	2*R*,3*R*	− 8.5	*M*
59	Ph	PhCO	H	O	2*R*,3*S*	−14	*M*
60	4-ClC_6H_4	PhCO	H	O	2*R*,3*S*	−13.5	*M*
61	Ph	2-Thienyl-CO	H	O	2*R*,3*S*	− 9.5	*M*
62	Ph	3-Thienyl-CO	H	O	2*R*,3*S*	− 9.5	*M*
63	Ph	H	H	O	2*R*	− 1.2	*M*
64	Ph	H	Me	O	2*R*,3*S*	− 0.9	*M*
65	Me	Me	H	O	2*R*,3*R*	+ 0.5	*P*
66	Me	Me	H	S	2*R*,3*R*	+ 0.5	*P*

[a] [μm^{-1} mol^{-1}].

Two types of information can be obtained[86-88]:

If the orientation of the long axis of the guest molecule is known, data concerning the electronic states involved becomes available.

If the polarizations of the transitions are known, their orientation with respect to the nematic director can be established.



55

63

The linear dichroism[85] of racemic **55** and **63** in the nematic phase ZLI 1167 shows that the molecule **55** is aligned with the long axis parallel to the nematic director, while **63** behaves approximately like a disk-shaped molecule: orientation of the phenyl group with its long axis parallel to the director is slightly favored.

The higher twisting power of **55** in MBBA than in any other liquid crystal is the result of close structural and conformational analogies (cf. Table 14). Several reports on phenyloxiranes reveal a preferred conformation for such a molecule. An X-ray structure analysis of 1-(4-bromophenyl)-1,2-epoxycyclohexane demonstrated that the phenyl group adopts a quasibisected conformation in the crystal[89]. MO calculations on phenyloxirane **63**[90] likewise point to a quasi-bisected conformation, with the plane of the phenyl group rotated towards the C–O bond of the oxirane ring. In this type of conformation the two aryl groups of (*R*,*R*)-(+)-*trans*-stilbene oxide **56** and analogous molecules are distorted and display a sort of left-handed two-bladed propeller helicity (Fig. 7).

It is quite interesting to note that the chirally distorted conformation (*M*-helicity) of substituted stilbene oxide fits very well into an *M*-distorted conformation of MBBA (Fig. 7).

This may explain the process of chirality transfer from the optically active solute such as **55** and **56** to the solvent such as MBBA: the chiral conformation of the solute as

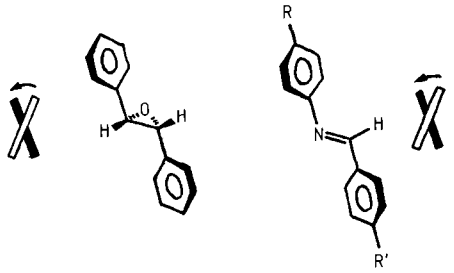
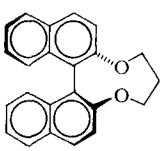


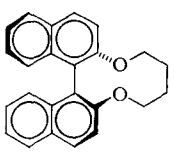
Fig. 7. Similarity between *trans*-diaryl epoxides such as **56** and MBBA **1**, R = *n*Bu, R' = MeO.

well as its analogy with MBBA may induce a chiral conformation of the solvent, and thus the formation of the cholesteric helix. Modification of the inducing compounds decreases their similarity to MBBA and thereby reduces the dynamic interactions with the solvent molecules; consequently the twisting power should decrease drastically, e.g., in globular molecules such as **63**.

In order to confirm this model, the compounds **29-31** and **67-76**, having a chiral cyclic binaphthyl or biphenyl structure with non-planar conformation and distinct helical configuration, were investigated[91]. Because of their biaryl geometry, the highest twisting powers were expected to occur in biphenyl-type nematic phases, which was indeed found to be the case for **30** and **31** (Table 16).



(*S*)-(+)-**30**



(*S*)-(+)-**31**

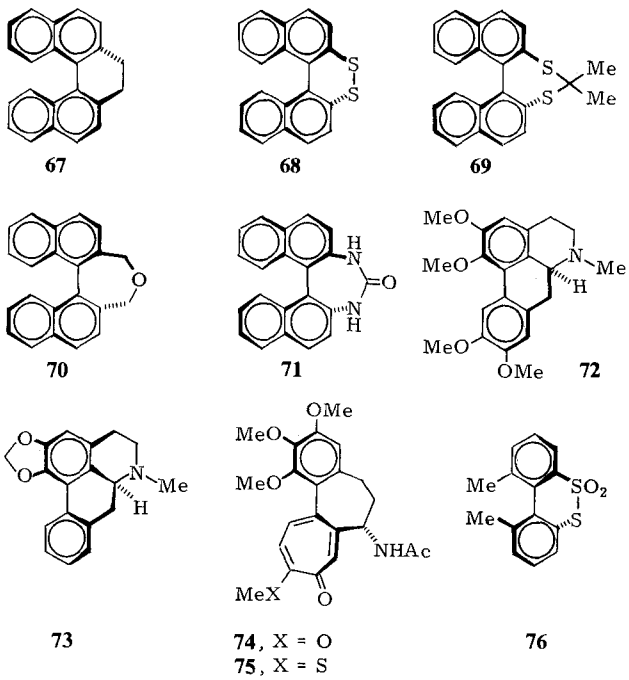
Table 16. Twisting powers β_M of the chiral binaphthyl derivatives **30** and **31** in nematic liquid crystals.

Liquid crystals		Type	β_M [μm^{-1} mol^{-1}] **30**	**31**
3	PCB	Biphenyl	+79	+80
1	MBBA	Schiff base	+65	+56
	1052	Aromatic ester	+42	+38
	ZLI 1167	Bicyclohexyl		+35

On the strength of this finding, the chiral compounds **29-31** and **67-76** were studied in biphenyl-type nematic phases (Table 17). All the absolute configurations are expressed in terms of helicity.

It is certainly gratifying to notice from Table 17 that, despite the important differences in the chemical structures of the compounds, *P*-helicity or *M*-helicity always leads to positive or negative values, respectively, for the twisting power (i.e. to right-handed or left-handed helices). In other words, the main factor determining the chirality of the induced mesophase is the twist sense of the biaryl moiety.

The very high values of β_M were somehow expected, since bridged biaryl compounds are conformationally ri-



67 68 69

70 71 72

73 74, X = O 75, X = S 76

Table 17. Twisting powers β_M of the chiral biaryl derivatives **29–31** and **67–76** in liquid crystals of the biphenyl type [91].

Chiral compound	Biaryl helicity	β_M [a]	Chiral compound	Biaryl helicity	β_M [a]
(*S*)-(+)-**67**	*P*	+69 [b]	(*S*)-(+)-**31**	*P*	+79 [c]
(*R*)-(−)-**68**	*M*	−65 [b]	(*S*)-(+)-**67**	*P*	+ 8 [b]
(*R*)-(−)-**69**	*M*	−71 [b]	(*S*)-(+)-**73**	*P*	+24 [b]
(*R*)-(−)-**70**	*M*	−55 [c]	(*S*)-(−)-**74**	*P*	+54 [b]
(*R*)-(−)-**71**	*M*	−21 [b]	(*S*)-(−)-**75**	*P*	+64 [b]
(*S*)-(+)-**29**	*P*	+85 [c]	(*R*)-(−)-**76**	*M*	− 5 [b]
(*S*)-(+)-**30**	*P*	+80 [c]			

[a] [μm^{-1} mol^{-1}]. [b] Nematic phase E_7: mixture of 4′-aryl- and 4′-*n*-alkyl-4-biphenylcarbonitrile. [c] PCB **3**.

gid, and, being structurally very similar, should interact very well with the biphenyl-type liquid crystals.

Furthermore, it was shown[91] by linear dichroism measurements that the binaphthyl **31** was oriented with the axis joining the two naphthyl groups parallel to the nematic director, i.e. to the long axis of the molecules in the nematic phase.

In nematic liquid crystalline solution, 4,4′-disubstituted biphenyl derivatives show non-planar conformations with torsion angles of 30 to 80°, depending on the substituents[92,93]. It is therefore reasonable to assume that such non-planar conformations exist also in biphenyl-type liquid crystals such as PCB **3** or E_7. In the nematic phase, pairs of mirror-image conformations are equally probable, but rapidly interconvert. The chiral biaryl inducer, with its biaryl axis aligned parallel to the biphenyl axis of the solvent, can have close contact and interact only with molecules having the same chirality (the same chiral conformation) (Fig. 8). At the very low experimental concentrations of the inducing compound it seems unrealistic, for statistical reasons, to postulate a model in which one molecule of solvent interacts with two molecules of solute. The chirality is therefore transferred from the inducer to a near molecule of solvent and from this to the next near one and so on, via *chiral conformations*. A biaryl derivative with *P*-helicity leads to a cholesteric phase of the same P-helicity.

These findings underline the importance of conformational effects on the twist mechanism.

Fig. 8. Model for the interaction between chiral biaryl derivatives and nematic liquid crystals of the biphenyl type [91].

Therefore, as long as there is no ambiguity about the solute orientation in the liquid crystal matrix (linear dichroism is a very informative in this domain), models can be established from solute-solvent interactions to correlate absolute configurations and twist sense, the correlation being much more certain in the case of strong solute-solvent interactions, i.e. in the case of high twisting powers.

Finally, a few more words must be added about the complementary phenomenom, i.e. induction of optical activity by a cholesteric liquid crystal. It was already shown in Section 2 that it is possible to induce a Cotton effect within the absorption bands of achiral molecules with the aid of a cholesteric liquid crystalline solvent. It has also been shown[94–96] that optical activity can be chemically induced by running an asymmetric synthesis in a cholesteric solvent. Since the chirality transfer is mainly the results of solute-solvent interactions, only low enantiomeric excesses have been obtained so far.

5. Concluding Remarks

In recent years many modern analytical techniques have been modified in order to obtain stereochemical information. Historically, the method most commonly used for obtaining information about chirality was polarimetry. Circular dichroism (CD) and optical rotatory dispersion (ORD) are now more powerful than polarimetry. The introduction of chiral shift reagents in NMR spectroscopy was probably one of the most spectacular improvements in the field of enantiomeric purity determinations.

The results reviewed in this report show that the extreme sensitivity of liquid crystals to optical activity makes them suitable for stereochemical studies. It is possible by very simple experiments to detect low optical activities and to determine the kinetics of racemization. Important contributions have also been made to the correlation of absolute configurations: the liquid crystal technique resembles the NMR technique, correlating absolute configurations to chemical shifts induced by chiral complexes, or chromatography, correlating retention times to the configurations of diastereoisomeric species. A better understanding of the nature of the interactions between chiral molecules and liquid crystals should lead to better models for solute-solvent interactions, so that the liquid-crystal technique could some day complement the ORD and CD techniques.

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COMMUNICATIONS

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Isolation of the First Six- and Seven-Membered Selenium-Sulfur Rings and Mechanism of their Conversion into Other-Sized Rings**

By *Ralf Steudel** and *Eva-Maria Strauss*

Cyclic selenium sulfides Se_xS_y have previously only been isolated in the ring sizes $x+y=8$ or 12[1]. We now report the isolation of compounds SeS_5 and Se_2S_5 as well as the decomposition of Se_2S_5 in solution, for which we propose a novel mechanism that is also relevant to other chalcogen compounds.

Titanocene pentasulfide, which contains a TiS_5 ring, reacts smoothly with S_2Cl_2 to afford S_7[2a], and with Se_2Cl_2—as we have now found—just as smoothly to yield the analogous heterocycle 1,2-Se_2S_5[3a].

$$(C_5H_5)_2TiS_5 + Se_2Cl_2 \xrightarrow[20°C]{CS_2} Se_2S_5 + (C_5H_5)_2TiCl_2 \qquad (a)$$

1,2-Se_2S_5 could be detected in CS_2 solution by high performance liquid chromatography (HPLC) and isolated as needle-shaped, dark orange crystals (density 2.69 g/cm^3 (25°)[3b] by rapidly covering the solution with pentane and cooling to −78°C. The solid compound completely decomposes at 25°C in 5 h but can be stored for several months at −78°C with no sign of decomposition. Upon heating, decomposition occurs above 99°C and melting at 111–113°C.

The SeSe bond of Se_2Cl_2 is retained in 1,2-Se_2S_5 as unequivocally indicated by the Raman spectrum, which exhibits one SeSe stretching frequency and only two SeS stretching frequencies (Fig. 1). If the conformation observed in the S_7 homocycle[2b] is also assumed for the Se_2S_5 ring, the spectrum is only consistent with the isomer shown in Figure 1; the three other feasible isomers with a SeSe bond can be ruled out for the following reasons: The two SeS stretching frequencies (339 and 304 cm^{-1}) are, respectively, 30 and 65 cm^{-1} wavenumbers lower than in SeS single bonds (e.g. in the rings Se_nS_{8-n}[4]) and must, therefore, be associated with two weak (long) bonds. These can only be the two bonds which in S_7 are 210 and 218 pm long and are, therefore, markedly longer than an SS single bond (205 pm). In contrast, for the SeSe stretching frequency of Se_2S_5 (271 cm^{-1}) a somewhat larger value is found than for a single bond (250 cm^{-1}); this can be accounted for by the conformation shown, since the corresponding bond in S_7 is slightly shorter than a single bond. The four SS stretching frequencies of Se_2S_5 appear at almost the same

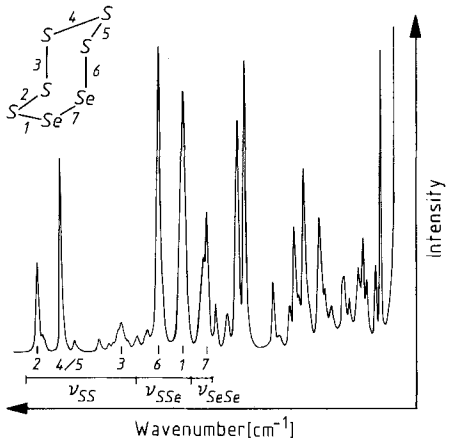

Fig. 1. Correlation of molecular structure and Raman spectrum (−110°C) of 1,2-Se_2S_5. The bonds 1–7 lead to the Raman lines of corresponding numbers (4 and 5 are the symmetric and asymmetric SS stretching frequencies of the bonds 4 and 5, respectively). Wavenumbers [cm^{-1}]: *511*, 505, *479*, 459, 425, 393, 372, 357, *339*, *304*, 276, *271*, 259, 242, *228*, *219*, 179, 155, *149*, *136*, *113*, 98, 79, 72, 59, *52*, 47, 34, *27* (most intense lines are shown in italics). Due to the different sizes of the S and Se atoms, bonds 2 and 7 are probably not coplanar, in contrast to S_7, i.e. the torsion angle at the bond 1 differs from zero.

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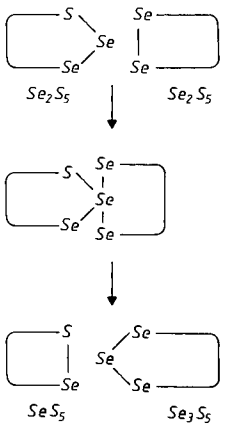
wavenumbers as the corresponding stretches of S_7[5]. Since a clear relation exists between the wavenumber $\tilde{\nu}_{SS}$ and the nuclear separations of the associated bonds[6], the SS bonds in Se_2S_5 must be almost as long as the corresponding bonds in S_7.

Reversed phase HPLC on octadecylsilane[7] indicates that Se_2S_5 decomposes in CS_2 solution at 25 °C according to

$$2\ 1,2\text{-}Se_2S_5 \longrightarrow SeS_5 + 1,2,3\text{-}Se_3S_5 \qquad (b)$$

At a concentration of 1 mmol/L the half-life of the reaction is ca. 1 h; disproportionation is complete after 2.5 h. Whereas the eight-membered ring Se_3S_5 has been isolated previously, we have now been able to obtain small amounts (ca. 20 mg) of the six-membered ring SeS_5 by cooling (−78 °C) a solution whose HPLC exhibited peaks of approximately the same size for the three rings in equation (b); the crystals were subsequently sorted according to their shape under the microscope. During this process Se_2S_5 remains in solution, Se_3S_5 crystallizes as orange needles, and SeS_5 is obtained as yellow, square crystals—similar to S_6 and Se_6, which are both known in pure crystalline form. The Raman spectrum of SeS_5 can be assigned to a six-membered ring with two SeS bonds[9]. As expected, the HPLC retention times of the compounds increase with the ring size: SeS_5 2.95, Se_2S_5 3.4, Se_3S_5 4.7 min (dead time 1.4 min; eluent: methanol/cyclohexane 90/10 v/v).

Formation of SeS_5 and 1,2,3-Se_3S_5 from 1,2-Se_2S_5 can be accounted for by the reaction mechanism shown in Scheme 1, in which a spirocyclic intermediate structurally related to SeF_4 is postulated. This species forms by insertion of an Se atom into the reactive SeSe bond of a second molecule and subsequent decomposition to SeS_5 and Se_3S_5, a reaction of this type is allowed by orbital symmetry.



Scheme 1.

Sulfur homocycles probably interconvert in an analogous way upon heating in CS_2 solution to 130–155 °C[10] or in the melt[11]; the corresponding interconversion of the selenium homocycles Se_8, Se_7, and Se_6 proceeds rapidly in solution even at 20 °C[12], and can be explained by the higher reactivity (lower bond energy) of the SeSe single bond. Decomposition, i.e. interconversion of sulfanes R–S_n–R (R = H, halogen, organyl) involving alteration of the chain length n, probably proceeds via a sulfurane SX_4 as reactive intermediate[13]. The mechanism proposed here thus deals with an important type of reaction in the chemistry of chalcogens.

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[3] a) *Procedure:* Cp_2TiS_5 (4.1 g) was stirred in 200 mL anhydrous CS_2 for 15 min and a solution of 1 mL Se_2Cl_2 in 50 mL CS_2 then added dropwise over 1 min. The precipitated Cp_2TiCl_2 (2.4 g) is filtered off and the filtrate cooled to −78 °C; 2.35 g Se_2S_5 (61% yield) crystallizes out within 24 h and is recrystallized three times from CS_2/pentane.—b)Lattice constants (−100 °C): $a = 1331.3$, $b = 1227.7$, $c = 434.2$ pm (orthorhombic), $Z = 4$, $\rho_{calc} = 2.98$ g/cm^3; the structure is disordered). Prof. *J. Pickardt* is thanked for these data.
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^{15}N-^{15}N Coupling Constants and Rotational Barriers of Nitrosamines**

By *Heinz Bandmann, Peter Heymanns, Carola Siem,* and *Paul Rademacher**

The spin-spin coupling constant ^1J characterizes the electron distribution in the individual bonds of a molecule[1]. Whereas because of the predominance of the Fermi contact term simple relations exist between ^1J and the electronic structure of the respective bonds for ^{13}C-H and ^{13}C-^{13}C coupling constants, for example, a correlation of this type for NN bonds is still not completely unequivocal due to the orbital and spin-dipolar terms, which can no longer be neglected, as well as the different influences of the lone pairs of electrons[3]. We have now found that for nitrosamines[4] linear correlations exist between the ^{15}N-^{15}N coupling constants and the π bond order of the NN bond, as well as with calculated values for the barrier to internal rotation ΔH^*.

Compounds **1**–**6**, whose NO group is ^{15}N-labeled (99%), were studied; the amino group contains ^{15}N in natural abundance[5]. The results are summarized in Table 1. Within experimental error, the δ-values for **1**, **4**, and **5** are in accord with those measured by *Gouesnard* and *Martin*[7] on unlabeled compounds; however, for **6** we found larger deviations[7]. According to theoretical investigations[8], ^1J is negative. For 1-phenylpyrazole, whose NN bond is similar to those in nitrosamines, $^1J_{N,N} = -12.91$ Hz was found[9]. We determined the absolute values.

As indicated by the resonance structures $R_2N-N=O$ and $R_2N^{\oplus}=N-O^{\ominus}$, the NN bond in nitrosamines exhibits

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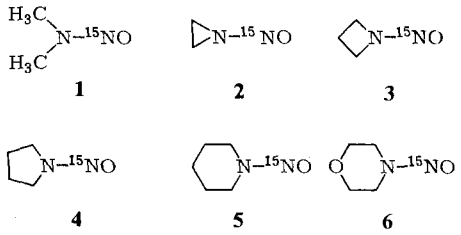

1 2 3 4 5 6

Table 1. ^{15}N-NMR study of **1**–**6**; conditions and results [a].

Compound	Solvent	conc. [wt.-%]	$\delta(N^1)$ [b]	$\delta(N^2)$ [b]	$^1J(^{15}N\text{-}^{15}N)$ [c] [Hz]
1	[D$_6$]acetone	68	231.5	535.4	19.0
2	diethyl ether	4	199.6	660.7	25.2
3	[D$_6$]acetone	62	230.3	540.3	20.0
4	$CDCl_3$	35	256.4	534.2	18.8
5	$CDCl_3$	45	246.7	531.8	20.1
6	$CDCl_3$	38	238.1	533.8	20.5

[a] Varian XL 200 spectrometer at 20.28 MHz. Measurement temperature for **2**, −40°C, otherwise 23°C. INEPT pulse sequence (R. Benn, H. Günther, *Angew. Chem. 95* (1983) 381; *Angew. Chem. Int. Ed. Engl. 22* (1983) 350). [b] Relative to NH_3(l) at 25°C. External standard: nitromethane, conversion factor +380.23 Hz [6]. N^1 = amino-, N^2 = nitroso-N atom. [c] Error limits for **1** and **4** ±0.2 Hz, otherwise ±0.6 Hz.

partial double bond character. A measure of this was taken to be the rotational barrier of the NN bond determined by dynamic NMR spectroscopy[7, 10]. The contribution made by the polar resonance structure to the electronic ground state of the molecule is governed by the donor ability of the amino group. In this respect, for compounds **1**–**6** the ring size is of paramount importance[11]. If the ^{15}N-^{15}N coupling constant is a function of the electron distribution in the NN bond, a correlation should exist between ^1J and the π bond order as well as the rotational barrier and, possibly, also with other structural parameters, such as the NN bond lengths. A correlation between the ^{15}N-^{15}N coupling constants and structural parameters is, however, not possible since, to date, only the structure of **1** has been determined[12]. No correlation is apparent between ^1J and NN bond lengths calculated by the MNDO method.

The linear relationship expressed by equation (a), with correlation coefficient $r^2 = 0.91$, exists between ^1J and the π bond order p of the NN bond[13]. And an excellent correlation ($r^2 = 0.97$) is obtained with equation (b) for ^1J and the enthalpy of activation ΔH^* of rotation about the NN bond[13]. Since the experimental values of ΔH^*[7, 10] for **2** and **6** are not known and those for **1**, **4**, and **5** are equal within experimental error, for the relationship (b) we used ΔH^* values calculated by the MNDO method[14, 15].

$$p = 0.020\ ^1J + 0.91 \quad \text{(a)}$$

$$\Delta H^* = 1.44\ ^1J + 39.4\ \text{[kcal/mol]} \quad \text{(b)}$$

Hence, in nitrosamines both the ^{15}N-^{15}N coupling constant and the rotational barrier can be used as a measure of the NN double bond order. In particular, this may offer advantages for thermolabile compounds such as **2**[16], which are not suitable for dynamic NMR studies. Moreover, the relationships offer a further possibility of studying this class of substances which are important in view of their carcinogenic activity[17]. It remains to be established whether the relationships (a) and (b) only apply to nitrosamines or are more general.

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1, 62-75-9; **2**, 36368-43-1; **3**, 15216-10-1; **4**, 930-55-2; **5**, 100-75-4; **6**, 59-89-2.

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[3] J. M. Schulman, J. Ruggio, T. J. Venanzi, *J. Am. Chem. Soc. 99* (1977) 2045; J. M. Schulman, W. S. Lee, *J. Magn. Reson. 50* (1982) 142.
[4] Previously, ^{15}N-^{15}N coupling constants of nitrosamines have only been published for diphenylnitrosamine (22 Hz) and dibenzylnitrosamine (19.0 Hz).
[5] **1** and **3**–**6** were prepared using the method described for **1**: P. Rademacher, W. Lüttke, *Spectrochim. Acta 27A* (1971) 715. **2** was synthesized at −40°C in anhydrous ether from aziridine and [^{15}N] amyl nitrite in the presence of the stoichiometric amount of hydrogen chloride.
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[14] K. Kirste, P. Rademacher, *J. Mol. Struct. 73* (1981) 171.
[15] With the MNDO method using complete optimization of geometry, ΔH^* values of 12.56, 11.13, and 9.20 kcal/mol, respectively, were obtained for **4**, **5**, and **6**; other values [14]. The calculated ΔH^* values are considerably smaller than the experimental; however, structural effects are reproduced correctly.
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Synthesis of Tetrahydro-3-thienylacetic Acid Esters by Consecutive Photo-Induced Reactions**

By *Elke Anklam* and *Paul Margaretha**

Irradiation of five-membered cyclic α,β-unsaturated carbonyl compounds, such as 2-cyclopenten-1-one[1], 2(5*H*)-, and 3(2*H*)-furanones[2, 3] usually leads to formation of tricyclic dimers. In addition, in solvents such as 2-propanol or cyclohexane photoreduction products are also obtained[4]. The [2+2]-photocycloaddition of such enones to olefins is one of the most important preparative photochemical reactions[5].

2(5*H*)-Thiophenone **1**, which is readily accessible from thiophene[6], behaves quite differently. Upon irradiation ($\lambda = 300$ nm) of **1** in benzene or cyclohexane in either the presence or absence of olefins, no products are detected, even after long irradiation times. In contrast, irradiation of **1** in alcohols leads selectively and in good yields to the 4-mercaptocrotonates **2**[7]. The fact that the rate of formation of **2** from **1** is not lowered by addition of 2,5-dimethyl-2,4-hexadiene, suggests a reaction proceeding from the S_1 state of **1**.

Irradiation of **1** in alcohols *in the presence* of 2,3-dimethyl-2-butene leads, in turn, to formation of the 4,4,5,5-tetramethyltetrahydro-3-thienylacetates **3**[7]. In this case, a

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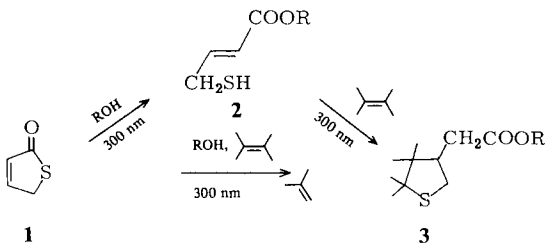
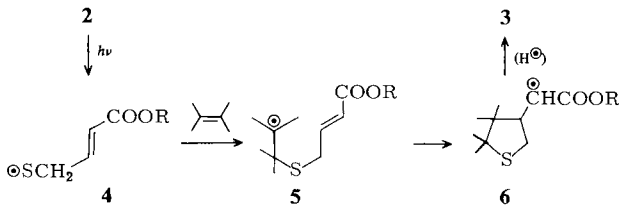
consecutive photoreaction is involved, since compounds **3** are also formed by irradiation of **2** in the presence of the olefin.



R = CH_3, C_2H_5, $(CH_3)_2CH$, $(CH_3)_3C$

The reaction **1*** + ROH → **2** involves photosolvolysis (ring opening does not occur in the dark). The esters **2**, which are readily accessible in this way, are interesting synthetic intermediates. The formation of **3** from **2** can be explained as follows: generation of the alkylthio radical **4** either by homolysis of the SH bond in the excited thiol[8] or H abstraction by the carbonyl oxygen of the ester group; stepwise [3 + 2]-cycloaddition[9] of **4** and olefin via **5** to afford the radical **6**; reaction of **6**, e.g., with **2** to give the final product **3**—in this case re-forming **4**.



This mechanism is corroborated by the results on the irradiation of **1** (or **2**) in the presence of 2-methylpropene. In this case, the products **8** analogous to **3** are formed; use of a large excess of olefin also leads to formation of the 2-(tetrahydro-3-thienyl)-4-methylpentanoic acid esters **11**. Alkylthio radicals add to olefins in *anti*-Markovnikoff orientation[8]. The fact that **8** (and **11**), but not the corresponding regioisomers, e.g. **9**, are formed exclusively suggests the involvement of an intermediate alkylthio radical. However, radical **7**, which is analogous to **6**, also reacts with 2-methylpropene to give **10** and, hence, compound **11**. The corresponding reaction of **6** with 2,3-dimethyl-2-butene does not occur—presumably for steric reasons. **8** and **11** can be separated by chromatography (SiO_2, CH_2Cl_2). The ^{1}H-NMR data of **2**, **3**, **8**, and **11** (in each case R = CH_3) are summarized in Table 1.

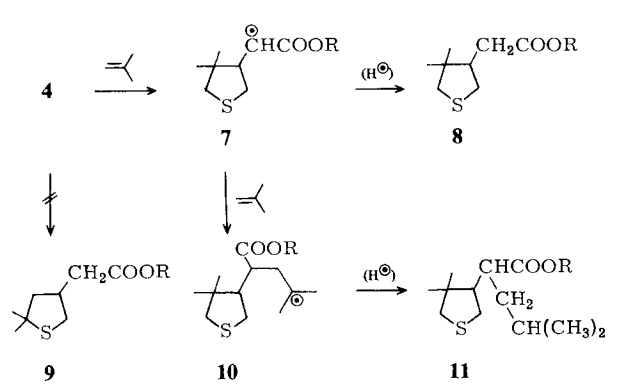
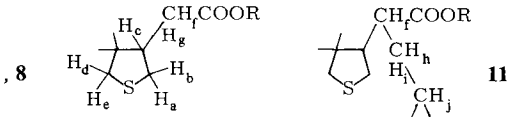


Table 1. 400 MHz-^{1}H-NMR data for compounds **2**, **3**, **8** and **11** (R = CH_3) in C_6D_6; δ-values, J in Hz.



2: 6.90 (d × t, J = 15.2, 7.2, 7.2), 5.77 (d × t, J = 15.2, 1.5, 1.5), 2.70 (m, J = 8.2, 7.2, 1.5, 2H), 1.15 (t, J = 8.2, SH)

3: H_a: 3.16 (d × d, J = 10.0, 7.0), H_b: 2.40 (d × d, J = 11.0, 10.0), H_c: 2.57 (m, J = 11.0, 10.4, 7.0, 3.8), H_f: 2.22 (d × d, J = 15.2, 3.8), H_g: 1.97 (d × d, J = 15.2, 10.4)

8: H_a: 3.16 (d × d, J = 10.6, 6.8), H_b: 2.50 (d × d, J = 10.6, 9.8), H_c: 2.10 (m, J = 11.0, 9.8, 6.8, 3.8), H_d: 2.46 (d, J = 10.2), H_e: 2.27 (d, J = 10.2), H_f: 2.16 (d × d, J = 15.6, 3.8), H_g: 1.85 (d × d, J = 15.6, 11.0)

11: H_a: 2.85 (d × d, J = 10.4, 7.0), H_b: 2.36 (d × d, J = 11.2, 10.4), H_c: 1.98 (d × d × d, J = 11.2, 9.6, 7.0), H_d: 2.67 (d, J = 10.5), H_e: 2.30 (d, J = 10.5), H_f: 2.42 (d × d × d, J = 12.2, 9.6, 3.8), H_h: 1.58 (d × d × d, J = 12.8, 12.2, 3.4), H_i: 0.97 (d × d × d, J = 12.8, 10.4, 3.8), H_j: 1.42 (m, J = 10.4, 3.4 and 6 × 6.4)

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[2] E. Anklam, P. Margaretha, *Helv. Chim. Acta 66* (1983) 1466.
[3] P. Margaretha, *Chimia 29* (1975) 203.
[4] P. Margaretha in Houben-Weyl: *Methoden der Organischen Chemie*, 4th edit., vol. 6/Ib, Thieme, Stuttgart, in press.
[5] P. Margaretha, *Top. Curr. Chem. 103* (1982) 1.
[6] R. T. Hawkins, *J. Heterocycl. Chem. 11* (1974) 291.
[7] *Procedure*: **2**: After 12 h irradiation (λ = 300 nm, Rayonet-RPR-100 photoreactor) of a N_2-degassed solution of **1** (1 g, 0.01 mol) in 100 mL alcohol, the solvent is distilled off. Unreacted **1** (40%) is separated from **2** (50—60%) by chromatography (SiO_2, Et_2O/pentane 1.1). Since at λ = 300 nm the extinction coefficient of **1** is only twice that of **2** (ε_{300} = 60), the yield of **2** is reduced at longer irradiation times.—**3**: A N_2-degassed solution of **1** (1 g) and 2,3-dimethyl-2-butene (5 g) in 100 mL alcohol is irradiated for 48 h. After removal of the solvent in vacuo, the residue is purified by kugelrohr distillation (150—160 °C/0.01 torr) (yield 80—85%).
[8] J. D. Coyle, *Chem. Soc. Rev. 4* (1975) 523.
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Enantioselective Synthesis of β-Substituted Primary Amines; α-Alkylation/Reductive Amination of Aldehydes via SAMP-Hydrazones**

By *Dieter Enders** and *Heinrich Schubert*

SAMP-hydrazones have proven to be useful reagents for the asymmetric synthesis of carbonyl compounds[1]. They allow, through alkylation, the formation of α-substituted aldehydes and ketones[2] and, through Michael addition, the synthesis of β-substituted δ-keto esters[3] with high enantioselectivity. Optically active amines are equally of interest as chiral building blocks and as compounds with a wide variety of biological activity.

We now report on the highly enantioselective synthesis of β-substituted primary amines **5**. The aldehydes **1** are

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converted into SAMP-hydrazones (*S*)-**2**, which are metalated with lithium diisopropylamide (LDA) in ether and alkylated with dimethyl sulfate or alkyl bromides to give **3**. According to ^{1}H-NMR shift experiments [methoxy singlet, Eu(fod)$_3$], the diastereomeric excess (*de*) is greater than 95%. Reduction with catecholborane (CB) in ether leads to the hydrazines **4**, whose reductive N–N cleavage with Raney nickel/hydrogen in methanol affords the β-substituted primary amines **5** in good overall yields (41–63%) (Table 1). (*S*)-2-methoxymethylpyrrolidine [(*S*)-**6**], which is also formed in this reaction, permits, after being separated off, the recovery of the chiral auxiliary SAMP[4] by nitrosation/reduction or *N*-amination with KOCN/Hofmann degradation[5]. The enantiomeric excesses of the amines **5** (*ee* ≥ 95%) are consistent with the *de* values obtained at the hydrazone stage **3**. They were determined polarimetrically (**5e**) and NMR spectroscopically via the 3,3,3-trifluoro-2-methoxy-2-phenylpropionamides (MTPA)[6] (^{19}F, ^{1}H) and by shift experiments with Eu(hfc)$_3$.

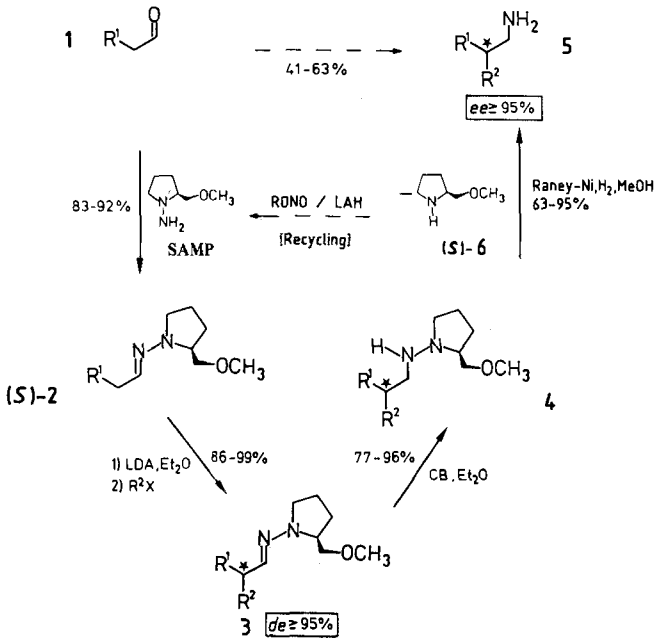

Table 1. Primary amines **5** prepared via SAMP-hydrazones from aldehydes **1** by alkylation/reductive amination.

5	R^1	R^2	B.p. [°C/torr] [a]	Total yield [%]	$[\alpha]_D^{22}$ (neat)	*ee* [%]
(*S*)-**5a**	CH_3	n-C_6H_{13}	75/15	63	− 8.4°	>95
(*R*)-**5a**	n-C_6H_{13}	CH_3		56	+ 8.1°	>90[b]
(*S*)-**5b**[c]	CH_3	$C_6H_5CH_2$	100–110/15	52	− 9.6°	>90[b]
(*R*)-**5b**	$C_6H_5CH_2$	CH_3		41	+10.8°	>95
(*S*)-**5c**	CH_3	$(CH_3)_2CH(CH_2)_3$	74/15	48	−10.6°[d]	>95
(*R*)-**5d**	n-C_9H_{19}	CH_3	78–84/1.5	53	+ 6.7°[e]	>95
(*R*)-**5e**	C_6H_5	CH_3	90/15	61	+32.7°[f]	95

[a] Data for short-path distillation. [b] According to NMR spectroscopic determination (MTPA-amides) *ee* ≥ 95%. [c] Alkylation in tetrahydrofuran. [d] $[\alpha]_D^{22}$ (c = 1.8, EtOH). [e] $[\alpha]_D^{22}$ (c = 1.1, C_6H_6). [f] $[\alpha]_D^{22}$ (c = 1.0, EtOH); (*S*)-**5e** [7]: $[\alpha]_D^{22} = -33°$ (c = 1.0, EtOH) corresponding to 96% *ee*.

Depending on the choice of nucleophilic and electrophilic building blocks, the C–C coupling procedure permits both enantiomers of an amine **5** to be prepared with high enantioselectivity by simply changing the priority of R^1 and R^2. This "opposite enantioselectivity by synthon control" is demonstrated in Table 1 for the enantiomeric pairs (*S*)-**5a**/(*R*)-**5a** and (*S*)-**5b**/(*R*)-**5b**. The absolute configurations of the new, optically active amines **5a–d** follow from the known selectivity in SAMP-hydrazone alkylations[1]; the absolute configuration of (+)-**5e** was already known[7].

The novel method of α-alkylation/reductive amination of aldehydes via SAMP-hydrazones[8] thus opens up an efficient and general entry to both optical antipodes of β-substituted amines **5** of high enantiomeric purity[10, 11].

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[7] H. Biere, C. Rufer, H. Ahrens, O. Loge, E. Schröder, *J. Med. Chem. 17* (1974) 716.
[8] *Procedure:* To a solution of 20 mmol LDA (from 12.5 mL 1.6 M *n*-butyllithium in *n*-hexane and 2.9 mL diisopropylamine) in 20 mL ether is added 20 mmol (*S*)-**2** under argon at 0°C and the mixture stirred for 4–5 h. After cooling to −120°C, the mixture is treated dropwise with R^2X, stirred for a further 3 h, and then allowed to warm to room temperature (RT). Work-up and distillation affords the hydrazones **3**, which are dissolved in 50 mL ether and treated under argon at 0°C with two equivalents of CB. Warming to RT within 12 h, washing with water and several times with 1 N NaOH, drying over $MgSO_4$, removal of solvent, and short-path distillation, affords the hydrazines **4**. These are dissolved in methanol (50 mL) and hydrogenated in a Parr hydrogenation apparatus with freshly prepared alkaline Raney nickel [9]/H_2 (3.5–3.8 bar, 20–40°C). After filtering off the catalyst, the filtrate is evaporated down, taken up in 50 mL ether, refiltered, treated with 1.5 equivalents of *p*-nitrobenzaldehyde, and stirred for 12 h at RT. The Schiff bases that are formed ($R_f \geq 0.9$) are separated from (*S*)-**6** ($R_f \leq 0.2 \rightarrow$ recycling) by column chromatography (SiO_2, ether); their ethereal solution (50 mL) is stirred with 50 mL 1 N HCl for 2 h. The aqueous phase is separated off, covered with a layer of ether (50 mL), and rendered alkaline with KOH pellets. After shaking, the ether phase is dried over $MgSO_4$, evaporated down, and the amines are distilled.
[9] *Organikum*, VEB Deutscher Verlag der Wissenschaften, Berlin 1977.
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[11] Enantioselective synthesis of α-substituted amines by asymmetric reduction or CN addition to SAMP/RAMP hydrazones: D. Enders et al., unpublished.

Configurational Stability of Vinyllithium Derivatives with 1-Trimethylsilyl and 1-Alkoxy Substituents**

By *Rudolf Knorr** and *Therese von Roman*

Considerable preparative interest[1, 2, 4] has been directed towards vinyllithium derivatives with silyl[1–3] and alkoxy[1, 4, 5] functions in the α-position. Qualitative observations on 1-silyl-1-alkenyllithium compounds (**1**, $R^1 = R_3Si$, $R^2 \neq H$) indicate that the *E*/*Z*-isomerization (**a** ⇌ **b**) in alkane solvents in the presence of 1,2-bis(dimethylami-

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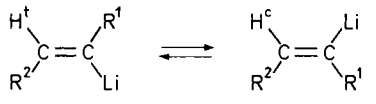
no)ethane (TMEDA) at +25 °C[3a] or in diethyl ether (Et_2O) above −35 °C[3b,c] occurs rapidly; only at temperatures below −65 °C is the configurational stability in ether[3c] and in tetrahydrofuran (THF)[2b,c] sufficient for stereospecific syntheses, but detailed rate data are not known. By direct observation of the *E/Z*-diastereotopomerization **1a** ⇌ **1b**[6] using dynamic NMR spectroscopy, we have now been able, for the first time, to determine the rate constants and activation parameters.



	R^1	R^2
1	$Si(CH_3)_3$	H
2	OC_2H_5	H
3	OCH_3	H
4	OC_2H_5	CH_3

The ^{1}H-NMR spectrum[8] of a THF solution[7] of 1-trimethylsilylvinyllithium **1** exhibits the AB splitting pattern of the olefinic CH_2 group (Table 1). As the solution was warmed to above room temperature, considerable line broadening was observed which was found to be reversible on cooling. Line-shape analysis[9] between +26 and +70 °C gave an activation enthalpy $\Delta H^{\neq} = 7.4$ (±1.5) kcal/mol and activation entropy $\Delta S^{\neq} = -32$ (±4) cal K^{-1} mol^{-1}. The half-life of the *Z/E* permutation in THF at +48 °C is therefore 0.11 s and, by extrapolation, ca. 0.5–15 min at −70 °C.

At room temperature, solutions of **1** decompose slowly (Table 1). In the absence of TMEDA, **1** cannot be generated in a similar way[7] in pentane; rather, as with the analogous (1-chlorovinyl)trimethylsilane[10], (3,3-dimethyl-1-butenyl)trimethylsilane is formed in addition to *tert*-butyltrimethylsilane. In TMEDA (by-product, *N,N*-dimethylvinylamine) the half-life of the *Z/E*-diastereotopomerization at +61 °C is considerably greater than 15 s. Since this solvent dependence and the previously mentioned activation parameters of **1** are in accord with those of 1-arylvinyllithium compounds[11], an ionic mechanism, as proposed[11] for the latter compounds, involving stabilization of charge by silicon[3c] can be presumed.

Table 1. ^{1}H-NMR data and stability of vinyllithium derivatives **1**–**4** in 0.05–0.5 M solutions, $\tau/2$ = half-life of the decomposition.

	Solvent	*T* [°C]	$\delta(H^t)$ [a]	$\delta(H^c)$ [a]	$^2J(H,H)$ [Hz]	$\tau/2$
1a, b	THF/HMPT [b]	25	7.28	6.90	9.5	20 min
1a, b	THF	+25	7.29	6.92	9.8	17 h
1a, b	THF	−41	7.26	6.81	11.0	—
1a, b	THF/alkane [c]	+25	7.32	6.96	9.5	6 d
1a, b	Et_2O/alkane [c]	+25	7.36	7.08	9.0	17 d
1a, b	TMEDA/alkane [c, d]	+25	7.45	7.18	9.5	3 d
2a, b	THF [e]	+25	4.87	3.93	0	≫ 15 h
2a, b	Et_2O/THF [f]	+25	4.91	4.06	0	≫ 2 d
2a, b	TMEDA [g]/alkane [h]	+25	5.07	4.47	[i]	—
3a, b	C_6D_6/THF [g]	[k]	5.39	4.56	0	[k]
4a, b	THF	+25	5.48 [l]	4.45 [m]	—	≫ 9 d
4a, b	[D_8]THF/TMEDA [g, n]	+25	5.44 [l]	4.32 [m]	—	≫ 17 h

[a] Assignments for **1**–**3** interchangeable. [b] With ca. 15 vol.-% hexamethylphosphoric triamide (HMPT). [c] Ca. 57 vol.-% pentane/hexane. [d] Same NMR parameters at +61 and −32 °C. [e] Almost the same δ-values with 50 vol.-% pentane at +25 and −50 °C, with $(CH_3OCH_2)_2$ or with 83 vol.-% TMEDA. [f] 20 vol.-%. [g] One mol. equivalent. [h] 90 vol.-% pentane/hexane. [i] Very broad. [k] Lit. [12a]. [l] q with $^3J = 6.5$ Hz (*E*-isomer). [m] q with $^3J = 6.0$ Hz (*Z*-isomer). [n] Methyl doublets at $\delta = 1.57$ (*E*) and 1.47 (*Z*), respectively.

1-Alkoxy-1-alkenyllithiums $R^2HC{=}C(OAlk)Li$[6] are formed and react in THF below −78 °C[4c, 5a, b] up to ca. −20 °C[5c] with retention of configuration; we investigated their previously unknown degree of configurational stability spectroscopically[8, 12]. The positions of the ^{1}H-NMR signals of the vinyl protons of 1-ethoxyvinyllithium **2**, which show up as sharp singlets in ethereal solutions[13], are consistent with the values given[12a] for **3** and are strongly solvent-dependent (Table 1); up to +106 °C, line broadening does not occur in TMEDA, but rather decomposition is observed. Since (*E*)-1-ethoxy-1-propene in the *E/Z* mixture[13] reacts considerably more rapidly with *tert*-butyllithium to afford **4a** than the (*Z*)-isomer to give **4b**, reduction of the amount of *tert*-butyllithium allows the selective formation of different *E/Z*-mixtures (1 : 3 to 3 : 1) of 1-ethoxy-1-propenyllithium **4**. *These ratios remain constant* for more than 13 days at +25 °C in THF; therefore, the compounds **4** (as well as **9**) are stable with respect to *Z/E*-isomerization.

We propose that the vanishingly small coupling constant of **2** and the unusually strongly positive one of **1** are due to the σ-inductive effects of R^1 and Li, which operate in opposite directions in **2** but in the same direction in **1**[14].

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[6] Compounds **1**–**4** are represented in simplified notation since neither their crystal structures nor their degrees of association in solution are known.

[7] *Experimental Procedure* for **1**: A solution of commercial (1-bromovinyl)trimethylsilane in 1.0 mL solvent is allowed to react with *tert*-butyllithium (1.5 M in pentane/hexane, 2.0 mmol) under N_2 at −74 °C until reaction is complete (2 h) [2d, f, 3c]. The lithium ethenolate formed in THF with tC_4H_9Li interferes in the spectroscopic investigation; solvent is therefore removed at 12 torr (room temperature) from a solution of **1** in Et_2O, and the residue is dissolved in THF at −25 °C. Injection of *tert*-butyl alcohol at −78 °C yields trimethylvinylsilane.

[8] Measured at 60 MHz after addition of ca. 15 vol. % $(CH_3)_4Si$ using a Varian HA-60 IL spectrometer.

[9] a) S. Alexander, *J. Chem. Phys. 37* (1962) 967, and literature cited therein; b) G. Binsch, *Top. Stereochem. 3* (1968) 97, see p. 113; c) Temperature dependence of the spectral parameters in ca. 0.4 M THF solution: $\delta(H^t) = 7.29 + 0.00046$ (T −298 K), $\delta(H^c) = 6.92 + 0.0017$ (T −298 K), $^2J(H,H) = 9.84 - 0.014$ (T −298 K).

[10] R. F. Cunico, Y. K. Han, *J. Organomet. Chem. 174* (1979) 247.

[11] R. Knorr, E. Lattke, *Tetrahedron Lett. 1977*, 3969.

[12] a) ^{1}H-NMR of **3**: J. A. Soderquist, G. J.-H. Hsu, *Organometallics 1* (1982) 830; b) ^{13}C-NMR of **2**: F. T. Oakes, J. F. Sebastian, *J. Org. Chem. 45* (1980) 4959.

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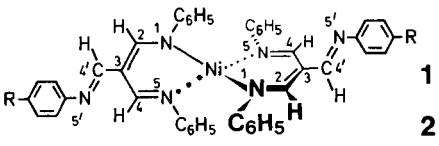
[13] *Experimental Procedure* for **2** and **4a/4b** (cf. [12a]): *tert*-Butyllithium (15–18 mmol in pentane/hexane) is added dropwise to a solution of 1-ethoxyethene (7.0 mmol) or of 1-ethoxypropene (*E*/*Z* = 28:72) in 10 mL THF (or 5.0 mL pentane with 7.0 mmol TMEDA) under an inert gas atmosphere at −74°C, the mixture allowed to warm slowly to room temperature, the solvent and educt removed at 12 torr/+25°C, and the residue taken up in fresh solvent. Signals of the regenerated enol ether (for **4a/4b** in the same *E*/*Z* ratio) appear in the ^{1}H-NMR spectrum only after addition of *tert*-butyl alcohol.

[14] R. Knorr, *Tetrahedron* 37 (1981) 929.

Detection of Intramolecular Linkage Isomerization of a (Pseudo)tetrahedral Nickel(II) Bis(chelate)**

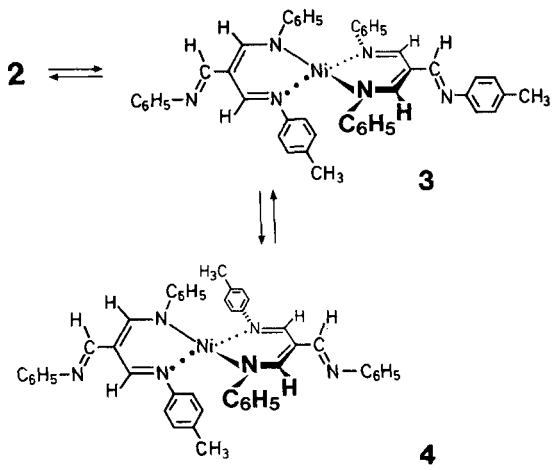
By *Rudolf Knorr** and *Friedrich Ruf*

The monomolecular interconversion of tetrahedral and planar isomers of tetracoordinated nickel(II) bis(chelates) such as **1** could proceed either as a thermally allowed, synchronous process[1] or, instead, in two steps involving reversible opening of a chelate ring. We found that a model (pseudo)tetrahedral nickel(II) compound[2] closely related to **1** undergoes slow inversion of configuration at 25°C[3,4], possibly involving transient formation of the planar (not detectable) form. We now wish to report that a spontaneous chelate opening is possible, using evidence of linkage isomerization of **2** to **3** and **4**.

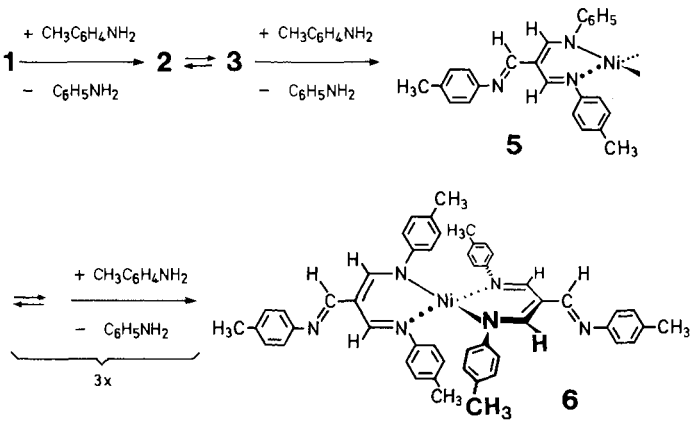


1: R = H

2: R = CH_3



Exchange of the two exocyclic phenylimino substituents of **1**[5] for *p*-tolylimino substituents, leading to **2**, is complete after less than 5 min at room temperature[6]. The ^{1}H-NMR spectrum[7a] of a solution of the purified nickel complex **2** in $CCl_4/DCCl_3$ (3:1) initially exhibits no extraneous signals; however, in the course of a few days at first one, and then a second, methyl singlet[7b] appear for **3** and **4**, arising from incorporation of the *p*-tolyliminomethyl groups into the chelate ring. In addition, a novel triplet for the *p*-hydrogen atom of the previously coordinated phenylimino group is observed. Consumption of **2** is measured by the reduction in intensity of the methyl signal of the exocyclic tolylimino groups and the *p*-absorption of the coordinated phenylimino groups[7a]. The final equilibrium of **2**, **3**, and **4** corresponds to the statistical distribution (1:4:4). The rate constant[8] $k_{iso} = 38(\pm 5) \times 10^{-8}\ s^{-1}$ at 24.5°(±1)°C refers to only one of the four equally probable linkage isomerizations of **2**. A parallel experiment using a twofold initial concentration yields the same value within experimental error; in this inert solvent the isomerization is, therefore, a first order reaction[9].



The very rapid formation of **2** from **1** permits an independent measurement of the rate constant under irreversible conditions. The ^{1}H-NMR spectrum recorded immediately after mixing the nickel complex **1** (0.175 M) with *p*-toluidine (3.73 M) in $DCCl_3$ shows only the nickel complex **2**. Intermediate products (e.g. **3**) of the linkage isomerization may be present in only very small steady-state concentrations, since they react immediately and almost completely with the remaining *p*-toluidine to form **5** by substitution of the now exocyclic phenylimino groups released from the chelate. The repeated interplay of bonding isomerization and exocyclic substitution leads eventually via three additional intermediates[8] to **6**, the sole final product[7c,10]. The increase in intensity of the methyl signal ($\delta = +26.6$) for the coordinated *p*-tolylimino group at the expense of that of the *p*-hydrogen signal of **2** ($\delta = -11.4$)[7a] was studied as a function of time and gave $k_{iso} = 64(\pm 20) \times 10^{-8}\ s^{-1}$, assuming the same rate constant for each of the conceivable linkage isomerizations. Within the limits of experimental error, this value is consistent with the forementioned rate constant and proves that free *p*-toluidine does not measurably accelerate the linkage isomerization.

Considering that the catalytically efficient donor property of *p*-toluidine should not be smaller than that of the solvents used in the two experiments, we suggest that the linkage isomerizations are initiated by *mono*molecular rupture of the N^5Ni bond in **2**[11].

Since the subsequent C^2C^3 rotation presumably contributes to the free energy of activation ($\Delta G^{\neq} = 26.0(\pm 0.3)$ kcal/mol) of the linkage isomerization, the similar values of k_{iso} and the rate constant for inversion of configura-

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tion[3] do not prove, but raise the possibility that a similar mechanism is involved for both reactions[9].

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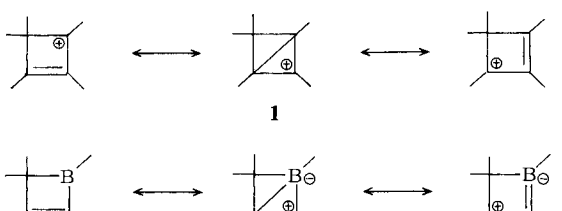
[1] E. A. Halevi, R. Knorr, *Angew. Chem. 94* (1982) 307; *Angew. Chem. Int. Ed. Engl. 21* (1982) 288; *Angew. Chem. Suppl. 1982*, 622.
[2] R. Knorr, F. Ruf, *J. Am. Chem. Soc. 101* (1979) 5424.
[3] Rate constant $6(\pm 2)\times 10^{-8}\ s^{-1}$ at 25°C in $DCCl_3$ (cf. [4]).
[4] F. Ruf, Dissertation, Universität München 1983.
[5] a) Ligand for **1**: R. Knorr, A. Weiss, *Chem. Ber. 115* (1982) 139; b) Nickel complex **1**, m.p. = 256–258°C: A. Weiss, Dissertation, Universität München 1976.
[6] *Experimental Procedure* [4]: *p*-Toluidine (420 mg, 3.9 mmol) is added to a solution of **1** [5] (100 mg, 0.14 mmol) in 5 mL of anhydrous CH_2Cl_2. After 5 min at room temperature, the solvent is quickly removed without heating using a rotary evaporator. The crystalline residue is precipitated from cold benzene solution by addition of anhydrous ethanol and washed thoroughly: Crude yield ca. 90% **2**, m.p. = 241.5–243°C.
[7] ^{1}H-NMR ($CDCl_3$, TMS int. standard): a) **2**: $\delta = +25.7$ (8 *m*-H from C_6H_5), +8.6 (2H-4'), +8.0 (4 *m*-H from *p*-tolyl), +6.7 and −2.2 (2 *p*-CH_3 and 4 *o*-H from *p*-tolyl), −6.6 and −11.4 (8 *o*-H and 4 *p*-H from C_6H_5).—b) Equilibrium mixture **2/3/4**: similar to **2** but with different intensities and additionally $\delta = +26.4$ (two unresolved methyl singlets from coordinated *p*-tolylimino) and +0.3 (t with $^3J = 7$ Hz, *p*-H from exocyclic C_6H_5).—c) **6**: $\delta = +371$ (2 H-2, 2 H-4), +26.6, and +25.6 (4 *p*-CH_3 and 8 *m*-H from coordinated *p*-tolylimino), +7.8, +6.7, and −2.2 (4 *m*-H, 2 *p*-CH_3, and 4 *o*-H from exocyclic *p*-tolyl), −6.7 (8 *o*-H from coordinated tolylimino).
[8] Formal kinetic formulation in [4].
[9] The problem of intermolecularity found for an octahedral cobalt(III) tris(acetylacetonate), designed with a similar concept, thus does not occur here: cf. J. P. Collman, J.-Y. Sun, *Inorg. Chem. 4* (1965) 1273; F. Basolo, R. G. Pearson: *Mechanisms of Inorganic Reactions*, 2nd edit., Wiley, New York 1967, p. 319, 320.
[10] Isolation of **6**: After removal of *p*-toluidine in vacuo, the residue is dissolved in anhydrous benzene and **6** precipitated by addition of anhydrous ethanol; m.p. (crude product) = 276–279°C.—Independent synthesis of **6**: yield 79%, m.p. = 296–298°C, spectra identical.
[11] Compare also the "swinging gate" mechanism of a planar Pd chelate which, however, involves solvent participation: W. G. Rohly, K. B. Mertes, *J. Am. Chem. Soc. 102* (1980) 7939.—Instead of an intermediate with tricoordinated nickel, one could, following the suggestion of a referee, also assume temporary formation of $\sigma(N^1)$-π(azaallyl)chelates in which the nickel atom is initially bonded to the $\pi(C^3C^4N^5)$- and then to the $\pi(C^3C^{4'}N^{5'})$-system. Differentiation between these two models is not yet feasible.

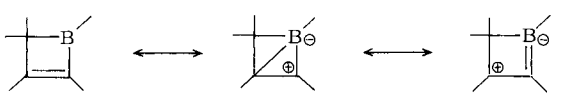
Strong 1,3-Interaction in 1,2-Dihydroboretes: Homoborirenes**

By *Rolf Wehrmann, Harmut Klusik,* and *Armin Berndt**

Cyclobutenyl cations **1** exhibiting 1,3-interaction have been described as homocyclopropenylium ions[1]. Herein we report on an experimental entry to the isoelectronic 1,2-dihydroboretes (boracyclobutenes) **2**, for which strong 1,3-interaction is demonstrated, so that the designation homoborirenes seems to be justified[2].



1



2

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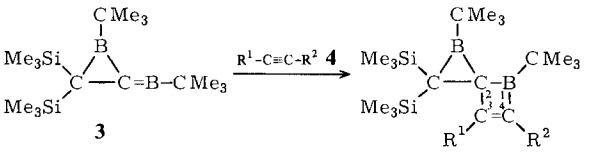
The 2-*tert*-butylborandiylborirane **3**[3] reacts with 2-butyne **4a** and 3,3-dimethyl-1-butyne **4b** below −50°C to give the 1,2-dihydroboretes **2a** and **2b**, respectively[4]. The addition of **4b** proceeds regioselectively, such that the *tert*-butyl group evades steric hindrance by a trimethylsilyl group of the three-membered ring. The structures of the compounds **2a** and **2b** follow from the ^{1}H-, ^{13}C- and ^{11}B-NMR spectra[5].



3 **2**

a: $R^1 = R^2 = Me$; **b**: $R^1 = H$, $R^2 = CMe_3$; **c**: $R^1 = R^2 = Ph$

The strong 1,3-interaction in **2a** and **2b** is concluded from the pronounced shielding of the boron atoms in the four-membered ring ($\delta = 34.5$ and 40 resp.), the shielding ($\delta = 143.2$ and 135.1, resp.) and broadening of the signals of the C^3 atom at 25°C, which indicate a bonding relation to B^1, and from the deshielding of the C^4 atom ($\delta = 185.5$ and 195.0, resp.). For normal interaction with a conjugated double bond, a chemical shift of ca. 75 is to be expected for the boron atom B^1, a *sharp* signal at ca. 175 at 25°C for the C^3 *not* bound to boron, and a chemical shift of ca. 140 ppm for the C^4 bound to boron[6].

In the case of the diphenyl derivative **2c**[3,4], neither the ^{11}B-NMR shift nor the broadening of the signal of C^3 can be measured at 25°C; the chemical shift of C^4, $\delta = 180.1$, however, indicates a strong 1,3-interaction.

The ^{13}C-NMR shift of C^4 in **2a** ($\delta = 185.5$) is as amazingly similar to the shift of a comparably substituted homocyclopropenylium ion ($\delta = 186.2$)[1b], as that of the ring C-atoms in the *tert*-butyl substituted borirenes to that in the tri-*tert*-butylcyclopropenylium ion[7].

2a and **2b** undergo transformation into products of still unknown structure more slowly than **2c**[3]. The low stability of **2a–2c** is consistent with the results of ab initio calculations[8], according to which the unsubstituted spirocyclic **2** represents a particularly energy-rich $C_4B_2H_6$ system.

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CAS Registry numbers:
2a, 89922-65-6; **2b**, 89922-66-7; **2c**, 87556-29-4; **3**, 87556-27-2; **4a**, 503-17-3; **4b**, 917-92-0; **4c**, 501-65-5.

[1] a) A. E. Lodder, J. W. Haan, L. J. M. Ven, H. M. Buck, *Recl. Trav. Chim. Pays-Bas 92* (1973) 1040; b) G. A. Olah, G. Liang, L. A. Paquette, W. P. Melaga, *J. Am. Chem. Soc. 98* (1976) 4327.
[2] A definition of homoaromaticity based on the electron density has recently been described: D. Cremer, E. Kraka, T. S. Slee, R. F. W. Bader, C. D. H. Lau, T. T. Nguyen-Dang, P. J. MacDougall, *J. Am. Chem. Soc. 105* (1983) 5069. According to this, in **1** and **2** with strong 1,3-interaction there is no 1,3-bonding but a large density concentration between the interacting centers; cf. D. Cremer, J. Gauss, P. von R. Schleyer, P. H. M. Budzelaar, *Angew. Chem. 96* (1984) 370; *Angew. Chem. Int. Ed. Engl. 23* (1984) 370.
[3] H. Klusik, A. Berndt, *Angew. Chem. 95* (1983) 895; *Angew. Chem. Int. Ed. Engl. 22* (1983) 877.
[4] Preparation of the homoborirenes: **2a**: A solution of **3** (100 mg, 0.33 mmol) in pentane is cooled to −50 to −60°C and treated with ca. 300 mg (5.5 mmol) **4a**. The mixture is allowed to warm to +20°C and excess **4a** and pentane removed by suction (oil pump).—**2b**: **4b** (ca. 40 mg, 0.5 mmol) is added to a solution of 100 mg (0.3 mmol) **3** in $CDCl_3$ (ca. 0.7 mL), cooled to −50 to −60°C in an NMR tube; NMR measurement of this sample at −40°C.—**2c**: prepared analogously to **2b** from **3**

(25 mg, 0.08 mmol) and **4c** (15 mg, 0.08 mmol); the conversion takes place within 1 h at −30°C in the NMR spectrometer.

[5] **2a**: colorless liquid, decomposition at room temperature ($\tau_{1/2} \approx 7$ d); ^{1}H-NMR ($CDCl_3$): $\delta = 2.05$, 1.76 (q, $^5J = 0.7$ Hz, each 3H, MeC=C), 1.20, 0.93 (s, each 9H, *t*Bu), 0.09, 0.06 (s, each 9H, $SiMe_3$); ^{13}C-NMR ($CDCl_3$, −35°C): $\delta = 185.5$ (s, 1C, C=*C*B, broad), 143.2 (s, 1C, *C*=CB), 53.6 (s, 1C, B*C*B, broad), 29.9, 28.1 (q, each 3C, *t*Bu), 27.7 (s, 1C, *C*Si_2, broad), 23.3, 20.8 (s, each 1C, *C*Me_3, broad), 16.4, 15.7 (q, each 1C, Me), 3.4, 2.5 (q, each 3C, $SiMe_3$); ^{11}B-NMR ($CDCl_3$): $\delta = 83$ (1B, $BCSi_2$), 34.5 (1B, BC=C).—**2b**: colorless liquid, decomposition at room temperature ($\tau_{1/2} \approx 12$ h); ^{1}H-NMR ($CDCl_3$): $\delta = 6.71$ (s, 1H, HC=C), 1.16, 1.11, 0.95 (s, each 9H, *t*Bu), 0.05, 0.04 (s, each 9H, $SiMe_3$); ^{13}C-NMR ($CDCl_3$, −40°C): $\delta = 195.0$ (s, 1C, C=*C*B, broad), 135.1 (d, ^1J(CH) = 165.5 Hz, 1C, H*C*=C), 56.5 (s, 1C, B*C*B, broad), 33.5 (s, 1C, C−*C*Me_3), 30.6, 30.1, 27.9 (q, each 3C, *t*Bu), 23.2, 20.0 (s, each 1C, B−*C*Me_3, broad), 3.8, 2.4 (q, each 3C, $SiMe_3$), the signal for *C*Si_2 must lie under the signal at 27.9; ^{11}B-NMR ($CDCl_3$): $\delta = 81$ (1B, $BCSi_2$), 40 (BC=C).

[6] Y. Yamamoto, I. Moritani, *J. Org. Chem. 40* (1975) 3434; K. Schlüter, Dissertation, Universität Marburg 1980; G. E. Herberich, B. Hessner, D. Söhnen, *J. Organomet. Chem. 256* (1983) C23. We thank Prof. *G. E. Herberich*, Aachen, for supplying the ^{13}C-NMR data of 2,3-Dihydroboroles.

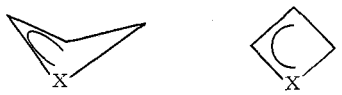
[7] C. Pues, A. Berndt, *Angew. Chem. 96* (1984) 306; *Angew. Chem. Int. Ed. Engl. 23* (1984) 313.

[8] P. von R. Schleyer, P. H. M. Budzelaar, private communication.

1,2-Dihydroborete: Structure of a Potential Homoaromatic System**

By *Dieter Cremer**, *Jürgen Gauss*, *Paul von Ragué Schleyer*, and *Peter H. M. Budzelaar*

Experimental and theoretical studies of cyclobutenyl cations **1** indicate that, due to relatively strong 1,3-interactions, the nonplanar form **1a** is more favorable than the planar form **1b**[1–3]. On the basis of quantum chemical model calculations, we now show that similar structural behavior is expected for 1,2-dihydroboretes **2**, which are isoelectronic to **1**.



a **b**

1, X = $CH^{\oplus}$
2, X = BH

Complete optimization of the geometry of **2** using the MINDO/3 method[4] leads to the nonplanar form **2a**, which is 6.1 (5.3) kcal/mol more stable than **2b**[5]. The corresponding value for **1** is 9.8 kcal/mol[3] (experimental value: 8.4 kcal/mol[1]).

Reinvestigation of the equilibrium structure determined for **2a** using ab initio calculations of the Hartree-Fock (HF) type with an extended 6-31G* basis set[6] led to the structural data summarized in Figure 1. Hence, the fold angle α in **2a** (152°, cf. Figure 1) is only slightly different from the calculated value of 148° for **1a** (HF/6-31G*[3]; exp.: 148.5°[2]). The 1,3-distance of 1.90 Å is somewhat longer than that in **1a** (HF/6-31G*: 1.79 Å[3]; exp.: 1.78 Å[2]). The relatively long B1C4 bond and the relatively short C3C4 bond indicate that delocalization of the two π electrons in the B1C4C3 region is not fully established[7].

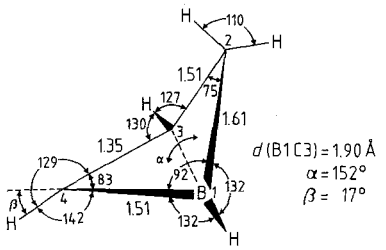


Fig. 1. Calculated structural parameters for the 1,2-dihydroborete **2a** (all values obtained from 6-31G* calculations; bond lengths [Å], bond angles [°]). The fold angle α is the angle between planes B1C2C3 and C3C4B1. Angle β measures the deviation of the bond vector C4H from the plane B1C4C3. Further parameters: B1H = 1.19, C4H = 1.07, C3H = 1.07, C2H = 1.08 Å, ∢ C2C3C4 = 103°.

The degree of 1,3-interaction can be determined by analysis of the one electron density distribution $\rho(r)$[8]. In proceeding from **2b** to **2a**, $\rho(r)$ between B1 and C3 increases by 20%; at the same time, the gross electron population at B1 and C3 grows, while that at C4 decreases. Although accumulation of $\rho(r)$ in the X1C3 region (X = B) is substantial, it is less than in **1a** (X = $C^{\oplus}$). This result, together with the inversion barrier calculated for **2a**, is an index for the 1,3-interaction, which is weaker than in **1**. In contrast to the homotropylium ion[8], accumulation of $\rho(r)$ between the interacting atoms in **1** and **2** does not lead to a saddle point in the electron density distribution[9].

In terms of an exactly defined model for homoconjugation based on the properties of $\rho(r)$, neither **1** nor **2** involve completely extended homoaromatic 1,3-bonding[8]; however, if the term *homoaromaticity* is used merely qualitatively to signify a change in structural and spectroscopic properties relative to those of a given reference state, without intending to specify quantitatively the difference between bonding and nonbonding 1,3-interactions, then both **1** and **2** can be described as homoaromatic[10].

Preliminary calculations with a minimal basis set (HF/STO-3G[11]) on the spirocyclic 1,2-dihydroborete **3**, several derivatives of which have recently been synthesized[12], also indicate a nonplanar structure for the dihydroborete ring (Fig. 2).

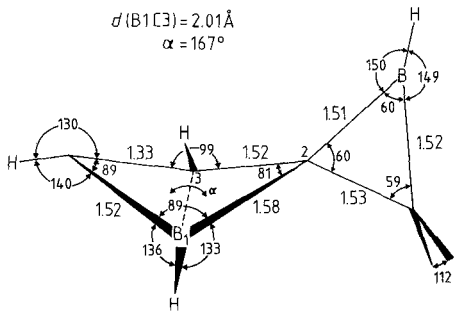


Fig. 2. HF/STO-3G parameters for the spirocyclic 1,2-dihydroborete **3** (bond lengths [Å], bond angles [°]). The fold angle α is the angle between the planes B1C2C3 and C3C4B1. Further parameters: B1H = 1.16, C3H = 1.09, C4H = 1.08, B5H = 1.15, C6H = 1.08 Å, ∢ C2C3H = 128, ∢ C4C3H = 132, ∢ B1C2B5 = 134, ∢ C3C2B5 = 131, ∢ B1C2C6 = 131, ∢ C3C2C6 = 129°.

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Since the endocyclic angle at C2 in **3** is strongly compressed, forcing the B1C2C3 angle to widen, the nonplanarity of **3** represents further evidence for the presence of strong 1,3-interactions in compounds of type **2**.

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[1] D. E. Applequist, J. D. Roberts, *J. Am. Chem. Soc. 78* (1956) 4012; E. F. Kiefer, J. D. Roberts, *ibid. 84* (1962) 784; G. A. Olah, J. S. Staral, G. Liang, *ibid. 96* (1974) 6233; G. A. Olah, J. S. Staral, R. J. Spear, G. Liang, *ibid. 97* (1975) 5489.

[2] C. Krüger, P. J. Roberts, Y.-H. Tsay, J. B. Koster, *J. Organomet. Chem. 78* (1974) 69.

[3] R. C. Haddon, K. Raghavachari, *J. Am. Chem. Soc. 105* (1983) 118 and literature cited therein.

[4] R. C. Bingham, M. J. S. Dewar, D. H. Lo, *J. Am. Chem. Soc. 97* (1975) 1285.

[5] The calculated ΔH_f^0 values are 9.5 (**2a**) and 15.6 kcal/mol (**2b**). Improvement of the MINDO/3 results by CI calculations (inclusion of all doubly excited configurations) leads to a slight reduction in the difference in energy between **2a** and **2b** from 6.1 to 5.3 kcal/mol.

[6] P. C. Hariharan, J. A. Pople, *Theor. Chim. Acta 28* (1973) 213.

[7] The calculated standard values for the BC-single and -double bond lengths are 1.57 and 1.34 Å, respectively: J. D. Dill, P. von R. Schleyer, J. A. Pople, *J. Am. Chem. Soc. 97* (1975) 3402.

[8] D. Cremer, E. Kraka, T. S. Slee, R. F. W. Bader, C. D. H. Lau, T. T. Nguyen-Dang, P. J. MacDougall, *J. Am. Chem. Soc. 105* (1983) 5069; R. F. W. Bader, T. S. Slee, D. Cremer, E. Kraka, *ibid. 105* (1983) 5061.

[9] In all molecules investigated to date (ca. 100), a saddle point in the electron density distribution $\rho(r)$ occurs between the bonded atoms, i.e. $\rho(r)$ possesses a minimum at a point between the atomic nuclei along the nuclear-nuclear axis, but has a maximum value for all directions perpendicular to this. Such a saddle point for $\rho(r)$ does not occur between the nonbonded atoms. This therefore suggests that the presence of a saddle point in $\rho(r)$ is associated with a chemical bond [8, 10].

[10] D. Cremer, E. Kraka, *J. Am. Chem. Soc.*, in press.

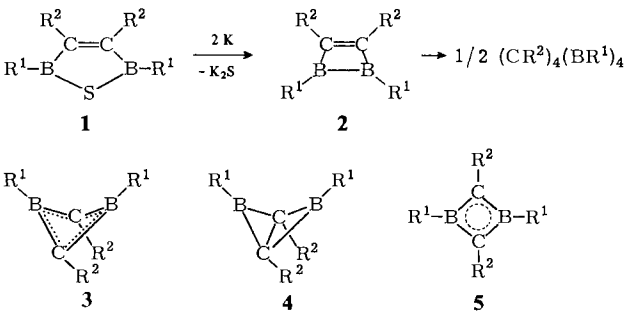
[11] W. J. Hehre, R. F. Stewart, J. A. Pople, *J. Chem. Phys. 51* (1969) 2657.—The calculated value for α represents an upper bound, since HF/STO-3G calculations underestimate ring folding: D. Cremer, *J. Am. Chem. Soc. 99* (1977) 1307.

[12] R. Wehrmann, H. Klusik, A. Berndt, *Angew. Chem. 96* (1984) 369; *Angew. Chem. Int. Ed. Engl. 23* (1984) 369.

Synthesis and Structure of a 1,3-Dihydro-1,3-diborete**

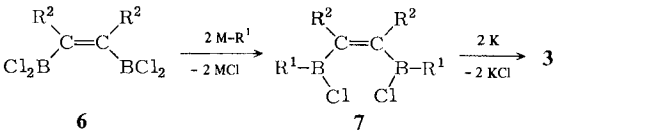
By *Manfred Hildenbrand, Hans Pritzkow, Ulrich Zenneck,* and *Walter Siebert**

We have postulated that desulfuration of the 2,5-dihydro-1,2,5-thiadiborole **1** (R^1 = Me, R^2 = Et) with potassium proceeds via an intermediary labile $(CR^2)_2(BR^1)_2$-molecule **2** which subsequently dimerizes to the *nido*-carbaborane $(CR^2)_4(BR^1)_4$[1]. However, attempts to stabilize the intermediate using electronically effective substituents in **1** only led to the formation of colored anions $\mathbf{1}^{\odot\ominus}$ and $\mathbf{1}^{2\ominus}$ (R^1 = OEt, O*i*Pr, OPh, Ph; R^2 = Et)[2].



1 **2** **3** **4** **5**

We report here on the first 1,3-dihydro-1,3-diborete **3a** (R^1 = NMe_2, R^2 = *t*Bu) whose structure has been elucidated by X-ray crystallography, and thus confirm the results of ab initio calculations[3] which indicate that the puckered four-membered ring **3** should be the most stable of the $(CR^2)_2(BR^1)_2$-isomers **2**–**5** (R^1 = R^2 = H). Reaction of B_2Cl_4 with 2,2,5,5-tetramethyl-3-hexyne (di-*tert*-butylacetylene) yields the *cis*-3,4-bis(dichloroboryl)-3-hexene derivative **6a** (R^2 = *t*Bu; yield 83%), which reacts with Me_3SiNMe_2 to give **7a** (R^1 = NMe_2, R^2 = *t*Bu; yield 70%). Dehalogenation of **7a** with K/Na in benzene (80°C, 75 h) leads to the formation of the colorless, relatively air-stable 1,3-dihydro-1,3-diborete **3a** (m.p. 68–70°C) in 65% yield.



6 **7**

The spectroscopic data[4] are consistent with the structure **3**. Since no C=C stretching vibration is observed in the Raman spectrum, and according to the NMR data (^{1}H, ^{13}C) the *N*-methyl groups are equivalent, a 1,2-dihydro-1,2-diborete **2** can be ruled out. In the ^{13}C-NMR spectrum, the signal for the ring C-atoms occurs at δ = 90.8, which is inexplicable in terms of either "unsaturated" (in **2**, cf. also **6a**) or "saturated" C-atoms (in the 2,4-diborabicyclobutane **4**); the chemical shift lies between those of the tetra-*tert*-butyl derivatives of cyclobutadiene (δ = 152.70) and tetrahedrane (δ = 10.20)[5]. On the basis of the ^{11}B-NMR spectrum (δ = 33.0), a diboratetrahedrane (as the first member of the *closo*-carbaboranes $(CH)_2(BH)_n$ with 10 skeletal electrons) can also be ruled out; the chemical shift, compared to that of other diorganoaminoboranes[6], suggests partial π-character in the BN and BC bonds. The ^{1}H-NMR spectrum shows no change in the singlets of the Me_2N and Me_3C substituents (δ = 2.92 and 1.11, respectively) in the temperature range −93 to +90°C. The mass spectrum shows the isotopic patterns expected for the molecular ion and the main fragments; a fragment with half the molecular mass is not observed. Reduction of **3a** with potassium in tetrahydrofuran yields a radical anion which shows a broad septet in the ESR spectrum (g = 2.0029, $a(^{11}B)$ = 10.3 G). This radical disappears after a short time at 20°C. An electrochemical reduction could not be achieved in CH_2Cl_2 up to −2.3 V.

Recently, on reacting di-*tert*-butylacetylene with $MeBBr_2$ and C_8K a mixture of products containing not only the corresponding borirene but also the 1,3-dihydro-1,3-diboretes **3b** and/or **5b** (R^1 = Me, R^2 = *t*Bu) has been obtained[7]. Other derivatives[8] give almost identical spectroscopic data as **3a**.

The X-ray structure analysis[9] shows a puckered ring structure for **3a**, which is in agreement with the calculations made for $(CH)_2(BR^1)_2$, R^1 = H[3] or NH_2[12]. A comparison with tetra-*tert*-butylcyclobutadiene shows that the bulky substituents in **3a** cannot be responsible for the strong puckering of the ring[10]. The molecule exhibits C_{2v} symmetry, and only the methyl groups deviate slightly

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therefrom (Fig. 1). The angle between the normals to the two planes through C1,B1,C2 and C1,B2,C2 is 52° (calculated values[3] 54.9, 48.2°). The dimethylamino groups lie almost in these planes (deviation 2–3°, calculated 5 and 6°), whereas the *tert*-butyl groups are shifted towards each other by about 12° (calculated 11.4 and 12.1°) from the planes through B1,C1,B2 and B1,C2,B2.

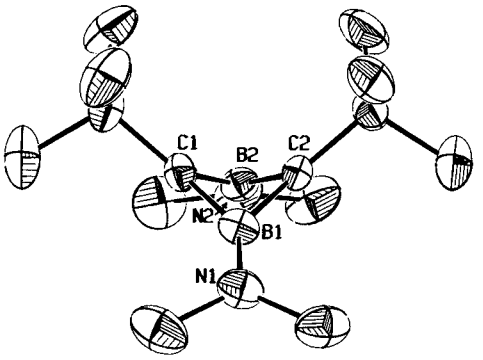

Fig. 1. Molecular structure of **3a** in the crystal. Vibrational ellipsoids correspond to 30% probability. Important distances [Å] and angles [°] (standard deviations 0.005 Å and 0.2°, resp.): C1–B1 1.501, C1–B2 1.503, C2–B1 1.505, C2–B2 1.506, C1–C2 1.814, N1–B1 1.415, N2–B2 1.404; B1–C1–B2 91.8, B1–C2–B2 91.6, C1–B1–C2 74.2, C1–B2–C2 74.2.

Due to the puckering, the C1–C2 distance in **3a** is reduced to 1.81 Å (calculated[3] 1.75 and 1.86 Å), while the B1–B2 distance of 2.16 Å is not much greater than in the planar ring **5**. The B–C distances of 1.50–1.51 Å (calculated[3] 1.48 and 1.51) are about 0.05 Å shorter than for single bonds. This suggests π-character in the four BC bonds, for which there are only two π-electrons available. On the basis of our findings (B–C 1.51, C···C 1.81 Å; $\delta(^{13}C)=90.8$) we favor a non-planar formulation **3** with delocalized π electrons rather than a diborabicyclo[1.1.0]butane structure **4**, for which C–C 1.40–1.50, B–C 1.55 Å and $\delta(^{13}C)=0$–20 are to be expected.

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[4] **6a** [11]: colorless crystals, m.p. 99–100°C; ^{1}H-NMR (C_6D_6): $\delta=1.20$ (s, 18H); ^{11}B-NMR (C_6D_6): $\delta=56.8$; ^{13}C-NMR ($CDCl_3$): $\delta=155.0$ (broad, 2C, C=C), 36.32 (s, 2C, CMe_3), 32.30 (s, 6C, CH_3).—**7a**: colorless crystals, m.p. 124–126°C; ^{1}H-NMR ($CDCl_3$): $\delta=2.78$ (s, 6H), 2.73 (s, 6H), 1.28 (s, 18H); ^{11}B-NMR (C_6D_6): $\delta=34.8$; MS: *m/z* 318 (M^+, 23%).—**3a**: ^{1}H-NMR ($CDCl_3$): $\delta=2.92$ (s, 12H), 1.11 (s, 18H); ^{11}B-NMR (C_6D_6): $\delta=33.0$; ^{13}C-NMR (C_6D_6): $\delta=90.8$ (broad, 2C, BCB), 43.22 (q, 4C, NCH_3), 32.68 (q, 6C, CH_3), 32.62 (s, 2C, CMe_3); MS: *m/z* 248 (M^+, 61.2%), 233 (M^+-CH_3, 100%), 69 (Me_3CC^+, 40%).
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[6] H. Nöth, B. Wrackmeyer: *NMR-Spectroscopy of Boron Compounds*, Springer-Verlag, Berlin 1978, p. 166–169.
[7] S. M. van der Kerk, P. H. M. Budzelaar, A. van der Kerk-van Hoof, G. J. M. van der Kerk, P. von R. Schleyer, *Angew. Chem. 95* (1983) 61; *Angew. Chem. Int. Ed. Engl. 22* (1983) 48. $\delta(^{11}B)$ is 35.9 or 38.5 for $(CtBu)_2(BMe)_2$, cf. [12].
[8] Cf. R. Wehrmann, C. Pues, H. Klusik, A. Berndt, *Angew. Chem. 96* (1984) 372; *Angew. Chem. Int. Ed. Engl. 23* (1984) 372.
[9] **3a** crystallizes in the monoclinic system, space group C2/c, $a=25.02(2)$, $b=9.02(1)$, $c=16.09(2)$ Å, $\beta=102.1(1)°$, $V=3549.0$ Å^3, $Z=8$; $R=0.068$ for 1512 independent reflections (Stoe two-circle diffractometer, $Mo_{K\alpha}$). Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD 50767, the names of the authors, and the full citation of the journal.
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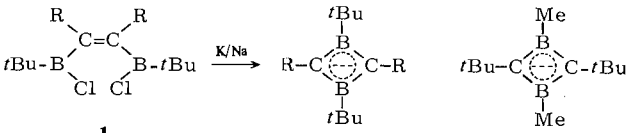
1,3-Dihydro-1,3-diboretes and Their Radical Anions**

By *Rolf Wehrmann, Christine Pues, Hartmut Klusik,* and *Armin Berndt**

1,3-Dihydro-1,3-diboretes **2** are derivatives of the, according to ab initio calculations, lowest energy $C_2B_2H_4$ system[1]. Experimentally, the 2,4-di-*tert*-butyl-1,3-dimethyl derivative **2e** was previously obtained in admixture with other compounds[2]. We report here on novel routes to 1,3-dihydro-1,3-diboretes and on their radical anions, which are isoelectronic with radical cations of cyclobutadienes[3].

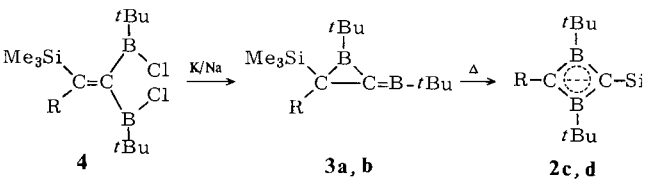
The derivative **2a**, isomeric with **2e**, can be prepared by reaction of the 1,4-dichloride **1a**[4a] with K/Na alloy in pentane. The analogous reaction of **1b**[4a] leads to **2b**[4b].



1 **2a, b** **2e**[2]

a: R = Me; **b**: R = Et

The derivative **2c** is formed in admixture with **3a** on reacting the 1,3-dichloride **4a**[4a] with K/Na alloy in boiling pentane. Heating the mixture to 170°C leads to isomerization of **3a** to **2c**. Correspondingly, **3b**[5] isomerizes to **2d** at 170°C ($\Delta G^{\ddagger}_{3\to 2}\approx 34$ kcal/mol).



4 **3a, b** **2c, d**

a, c: R = CH_2-*t*Bu; **b, d**: R = $SiMe_3$

The structure of the new compounds **2a**–**2d**[6] follows from the ^{1}H-, ^{13}C- and ^{11}B-NMR spectra and the Raman and mass spectra. The fragment ions with half the molecular mass observed in the mass spectra of **2e** (rel. int. 34%)

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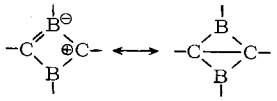
do not appear in the spectra of **2c** and **2d**, and only weakly in the spectra of **2a** and **2b** (rel. int. 2.6 and 1.4%, respectively). Since the Raman spectra of **2a—2d** do not contain bands in the region for CC double bonds, the structure of the isomeric 1,2-dihydro-1,2-diboretes can be ruled out.

Table 1. NMR shifts (δ values, $CDCl_3$) of the skeletal atoms of **2a—2d** and ESR coupling constants (in $G = 10^{-4}$ T) of the corresponding radical anions ($g = 2.0028$).

Cpd.	**2a**/**2a**$^{\odot\ominus}$	**2b**/**2b**$^{\odot\ominus}$	**2c**/**2c**$^{\odot\ominus}$	**2d**/**2d**$^{\odot\ominus}$	**2e** [2]
$\delta(^{11}B)$	41.2	40.3	42.4	45.0	35.9 or 38.5 [7]
$\delta(^{13}C)$	124.8	126.2	105.9 107.7	81.5	127—133 [2] 86.9 [7]
$a(^{11}B)$	9.5	9.4	9.4	8.9	—
$a(H)$	14.3	11.7	7.8	—	—
$a(^{29}Si)$	—	—	8.8	7.0	—

The chemical shifts for the boron and carbon atoms in the ring skeleton of **2** (Table 1) rule out the structure of a 2,4-diborabicyclobutane, for which $\delta(^{11}B) \approx 80$—as in the case of boriranes[5]—and $\delta(^{13}C) \approx 10$—as in the case of bicyclobutanes[8]—are to be expected. The shielding of the boron atoms reflects the π-charge density corresponding to **A** (one of four equivalent resonance formulas), while the shielding of the ring C-atoms compared to systems with partial positive charge on the carbon atom (1-*tert*-butylborirenes: $\delta(^{13}C) \approx 185$[9a], homoborirenes: $\delta(^{13}C) \approx 190$[9b]) reflects a 1,3-interaction corresponding to **B**.

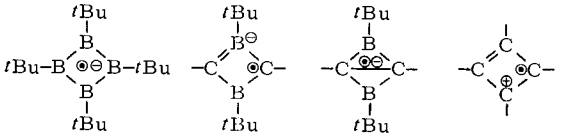


A **B**

This interaction has been predicted theoretically[1], and the puckering of the ring associated with it has been experimentally confirmed by an X-ray structure analysis of the 2,4-di-*tert*-butyl-1,3-bis(dimethylamino)-1,3-dihydro-1,3-diborete[10]. The increase in shielding of the ring C-atoms on successive replacement of alkyl by trimethylsilyl substituents is indicative of an increasing 1,3-interaction, and thus also of the puckering as a result of increasing steric hindrance.

The 1,3-dihydro-1,3-diboretes **2a—2d** can be reduced to radical anions with K/Na alloy in dimethoxyethane/tetrahydrofuran. The large ESR coupling constant of the methyl protons in **2a**$^{\odot\ominus}$ (14.3 G; cf. 26.9 G in $^{\circ}CH_2CH_3$) indicates that the unpaired electron resides almost exclusively on the carbon atoms of the ring. The large ^{11}B-coupling constants compared to those in **5**$^{\odot\ominus}$ ($a(^{11}B) = 1.2$ G)[11] must, therefore, be essentially due to spin polarization as a result of high spin density on C^2 and C^4, and must have negative signs. The electronic structure of the radical anions **2a**$^{\odot\ominus}$—**2c**$^{\odot\ominus}$ is thus described in terms of **C** (one of the four equivalent resonance formulas), 1,3-interaction corresponding to formulation **D** is not involved, the radicals are planar.

According to calculations[3a,12], the radical cations **6**$^{\odot\oplus}$ of cyclobutadienes, which are isoelectronic with **2**$^{\odot\ominus}$, are also planarized compared to the puckered dications **6**$^{2\oplus}$[13]. Strong steric hindrance leads to puckering and 1,3-interaction: The increase of $a(^{11}B)$ from -9.4 to -8.9 G and the decrease of a (^{29}Si) to 7.0 G in **2d**$^{\odot\ominus}$ compared to 8.8 G in **2c**$^{\odot\ominus}$ indicate a shift of spin density from the carbon to the boron. A four-membered ring structure deviating from planarity is also assumed for the strongly sterically hindered radical cation of tetra-*tert*-butylcyclobutadiene[3a].



5$^{\odot\ominus}$ **C** **D** **6**$^{\odot\oplus}$

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[6] **2a**: colorless liquid, b.p. 153 °C (yield 9%); ^{1}H-NMR ($CDCl_3$): $\delta = 1.94$ (s, 6H, Me), 1.05 (s, 18H, *t*Bu); ^{13}C-NMR ($CDCl_3$, -36 °C): $\delta = 124.8$ (s, 2C, BCB, broad), 28.8 (q, 6C, *t*Bu), 19.2 (s, 2C, BCMe_3, broad), 13.0 (q, 2C, Me); MS: *m/z* 190 (M^+, 9.1%), 175 ($M^+ - CH_3$, 14.1%), 133 ($M^+ - t$Bu, 100%), 106 ($M^+ - 84$, 59.9%).—**2b**: colorless liquid, b.p. 30 °C/0.6 torr (yield 30%); ^{1}H-NMR ($CDCl_3$): $\delta = 2.41$ (q, $J = 8$ Hz, 4H, CH_2), 1.05 (s, 18H, *t*Bu), 0.97 (t, $J = 8$ Hz, 6H, CH_3); ^{13}C-NMR ($CDCl_3$, -30 °C): $\delta = 126.2$ (s, 2C, BCB, broad), 29.3 (q, 6C, *t*Bu), 21.7 (t, 2C, CH_2), 19.0 (s, 2C, BCMe_3, broad), 16.6 (q, 2C, CH_3); MS: *m/z* 218 (M^+, 18.9%), 161 ($M^+ - t$Bu, 100%), 134 ($M^+ - 84$, 19.4%).—**2c**: colorless liquid, b.p. 56 °C/10^{-2} torr (yield: 58%); ^{1}H-NMR ($CDCl_3$): $\delta = 2.31$ (s, 2H, CH_2), 1.04 (s, 18H, B—*t*Bu), 0.82 (s, 9H, CH_2—*t*Bu), 0.16 (s, 9H, $SiMe_3$); ^{13}C-NMR ($CDCl_3$, -30 °C): $\delta = 107.7$, 105.9 (s, each 1C, BCB, broad), 42.0 (t, 1C, CH_2), 31.0 (s, 1C, CH_2—CMe_3), 29.4 (q, 6C, B—CMe_3), 29.2 (q, 3C, CH_2—CMe_3), 18.9 (s, 2C, BCMe_3, broad), 1.2 (q, 6C, $SiMe_3$); MS (27 eV): *m/z* 304 (M^+, 64%), 247 ($M^+ - t$Bu, 100%), 73 ($SiMe_3^+$, 33%).—**2d**: colorless crystals, subl. 80 °C/10^{-2} torr, m.p. 72—74 °C (yield ca. 90%); ^{1}H-NMR ($CDCl_3$): $\delta = 1.02$ (s, 18H, *t*Bu), 0.09 (s, 18H, $SiMe_3$); ^{13}C-NMR ($CDCl_3$, -42 °C): $\delta = 81.5$ (s, 2C, BCB, broad), 29.3 (q, 6C, *t*Bu), 18.6 (s, 2C, B—CMe_3, broad), 1.0 (q, 6C, $SiMe_3$); MS: *m/z* 306 (M^+, 74%), 291 ($M^+ - CH_3$, 77%), 249 ($M^+ - t$Bu, 89%), 73 ($SiMe_3^+$, 100%).
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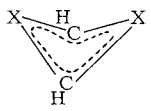
Puckered Structures of 1,3-Dihydro-1,3-diboretes and Bicyclobutane-2,4-dione: Nonplanar Hückel 2π-Electron Aromatic Molecules**

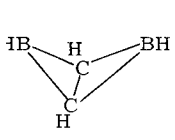
By *Paul von Ragué Schleyer**, *Peter H. M. Budzelaar*, *Dieter Cremer*, and *Elfi Kraka*

Krogh-Jespersen's[1a] calculational discovery that the cyclobutadiene dication prefers a puckered **1** rather than a planar structure initiated interest in the isoelectronic 1,3-dihydro-1,3-diborete **2**. Ab initio molecular orbital theory predicted a nonclassical folded geometry for this molecule as well[1b].



1, X = $CH^{\oplus}$
2, X = BH

Structure **2**, calculated (4-31G basis set) to have an unusual C–C distance of 1.86 Å, was favored over classical **3** and planar Hückel 2π aromatic **4** alternatives. The repulsive 1,3-interactions in **4** are reduced or eliminated in **2**. Due to orbital mixing, other electronic features of **2** are also more favorable than those in **4**[1b].



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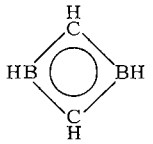

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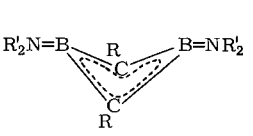
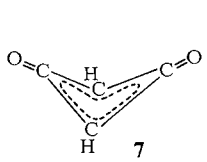


5, R = $C(CH_3)_3$, R' = CH_3
6, R = R' = H

Quite recently the first syntheses of 1,3-dihydro-1,3-diborete derivatives were achieved in three different laboratories[2–4], and the first X-ray determination carried out. *Siebert*'s puckered structure of **5**[4] is in remarkably close agreement with our 1981 predictions of **2** (Table 1). Thus the experimental distance, 1.81 Å, is much longer than the normal C–C bond length found in bicyclobutane (1.50 Å)[5]. The short exocyclic BN bonds in **5** (1.41 Å) indicate considerable B=N double bond character. Nevertheless, the very good π-donor $N(CH_3)_2$ substituents in **5** evidently alter the geometry of **2** only to a small extent. To examine this matter further, we have now calculated the structure of **6**, a simple analog of **5**, with the 3-21G basis set[6]. The geometry of **2** was redetermined at that level. The work has been further extended to the isoelectronic "organic" counterpart of **6**, bicyclobutane-2,4-dione **7**.



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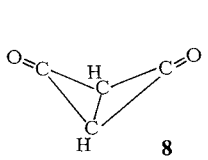

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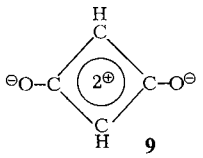

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As can be seen from the data collected in Table 1, the calculated structure of **6** agrees even more closely than that of **2** with the experimental structure of **5**[4]. The long C···C and the B=N distances are essentially identical, and the calculated puckering angle, α, is only 4° smaller than the experimental value. In view of the bulky substituents in **5**, better agreement could hardly be expected.

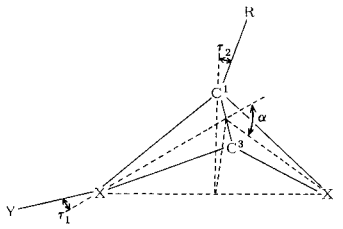

Table 1. Comparison of calculated and experimentally determined structures.

Compound	Data source [a]	Distances [Å] $C^1\cdots C^3$	C^1-X	Angles [°] HCC	α	τ_1	τ_2
1 (D_{2d})	4-31G opt. [1a]	1.973	1.431	160.6	35.8		1.5
	6-31G* opt. [1a]	1.928	1.414	157.1	42.6		1.6
2 (C_{2v})	STO-3G opt. [1b]	1.754	1.477	140.6	54.9	6.2	7.4
	4-31G part. opt. [1b]	1.858	1.510	141.0	48.2	5.2	11.4
	3-21G opt. [b]	1.883	1.521	141.4	47.6	5.1	11.5
5	exp. [4]	1.814	1.504 [c]	52		2–3	12
6 (C_{2v})	3-21G opt.	1.794	1.528 [d]	133.9	48.4	6.4	16.7
7 (C_{2v})	3-21G opt.	1.762	1.464 [e]	139.4	45.8	6.9	13.3
Bicyclo-butane	exp. [5]	1.497	1.498	128.3	58.3	−0.7	11.5
	3-21G opt.	1.484	1.513	134.7	61.8	1.4	3.0
	6-31G* opt. [f]	1.466	1.489	132.5	59.9	1.4	6.0

[a] The basis sets used for geometry optimizations are indicated. STO-3G is a minimal basis, 3-21G and 4-31G split valence bases, and 6-31G* a polarization basis. The accuracy of the results obtained at these levels are generally expected to increase in the order given. [b] T. Clark, unpublished. [c] BN distance 1.410 Å av. [d] BN distance 1.403 Å, CH 1.075, NH 1.000 Å; angles, BNH 122.6°; CBNH 171.8°. [e] CO distance 1.196 Å (in **9** 1.208 Å), CH 1.066 Å. [f] For 4-31G and 6-31G* geometries see K. B. Wiberg, *J. Am. Chem. Soc. 105* (1983) 1227.

The donation of ca. 0.2π electron from nitrogen to boron in **6** only results in a decrease of ca. 0.04 e in the C→B donation. The inversion barrier though the planar structure increases by 4 kcal/mol (**2** vs **6**) as a consequence, but the other effects are small. Because of the electropositive character of boron, other electronegative substituents (like OR or F) also are not expected to alter the geometry appreciably.

We now predict that bicyclobutane-2,4-dione **7**[7], like **1**, **2**, **5**, and **6**, will also prefer a nonclassical folded structure (Table 1). The 3-21G optimized central C1···C3 distance in **7** (1.76 Å) excludes the classical formulation **8**. This distance is halfway between that in bicyclobutane (1.50 Å)[5] and that calculated for planar **9** (2.01 Å). Analysis of the electron distribution $\rho(r)$ reveals a considerable build-up of negative charge between C1 and C3 in going from **9** to **7**. The properties of $\rho(r)$ in **7** are typical for a situation preceding the formation of a C–C bond[8]. The C–O electronegativity difference is nearly the same as that between B

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and N; the bonding situations in **6** and **7** are rather similar.

As suggested by the formal structure **9**, a planar form would be expected to benefit from the Hückel 2π character of the four-membered ring. Nevertheless, **9** is 14.6 kcal/mol less stable than **7** with the larger 6-31G* basis set (13.2 kcal/mol; 3-21G). The inversion barrer for **6** is indicated to be even larger, 20.6 kcal/mol (6-31G*//3-21G; 18.4 kcal/mol, 3-21G). According to the properties of $\rho(r)$, electron delocalization in puckered **6** and **7** is still large and is supported by the now favorable 1,3-interaction. Both π and σ effects contribute to the stability of the puckered forms[1]. Once again, our calculational observations emphasize that an aromatic 2π electron ensemble does not necessarily imply planarity of a four-membered ring like **1**, **2**, **5**, or **6**.

Our results on **7** are pertinent to a large number of squaric acid derivatives, e.g., the "squaraines" ("quadrains")[7]. While examples with good π donor substituents are planar[9], we are attempting to find cases with non-planar structures. Groups with C=N or C=C double bonds[10] when substituted at C2 and C4 of bicyclobutane may also lead to partially opened structures like **7** with elongated C1–C3 bonds[11].

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[1] a) K. Krogh-Jespersen, P. von R. Schleyer, J. A. Pople, D. Cremer, *J. Am. Chem. Soc. 100* (1978) 4301; J. Chandrasekhar, P. von R. Schleyer, K. Krogh-Jespersen, *J. Comput. Chem. 2* (1981) 356; b) K. Krogh-Jespersen, D. Cremer, J. D. Dill, J. A. Pople, P. von R. Schleyer, *J. Am. Chem. Soc. 103* (1981) 2589.

[2] S. M. van der Kerk, P. H. M. Budzelaar, A. van der Kerk-van Hoof, G. J. M. van der Kerk, P. von R. Schleyer, *Angew. Chem. 95* (1983) 61; *Angew. Chem. Int. Ed. Engl. 22* (1983) 48.—Repetition of this work leads to a revised value, $\delta(^{13}C)=86.9$ ppm, for the ring carbon; $\delta(^{11}B)$ is at 35.9 or 38.5 ppm, the other value corresponding to the borirene.

[3] R. Wehrmann, C. Pues, H. Klusik, A. Berndt, *Angew. Chem. 96* (1984) 372; *Angew. Chem. Int. Ed. Engl. 23* (1984) 372.

[4] M. Hildenbrand, H. Pritzkow, U. Zenneck, W. Siebert, *Angew. Chem. 96* (1984) 371; *Angew. Chem. Int. Ed. Engl. 23* (1984) 371.

[5] See P. G. Gassman, M. L. Greenlee, D. A. Dixon, S. Richtsmeier, J. Z. Gougoutos, *J. Am. Chem. Soc. 105* (1983) 5865 and literature cited therein.

[6] The Gaussian 80 series of programs were employed. J. S. Binkley, R. A. Whiteside, K. Raghavachari, R. Seeger, H. B. Schlegel, D. J. DeFrees, S. Topiol, L. R. Kahn, J. A. Pople, *QCPE 13* (1981) 406.

[7] See R. Gleiter, R. Hoffmann, *Angew. Chem. 81* (1969) 225; *Angew. Chem. Int. Ed. Engl. 8* (1969) 214; R. West: *Oxocarbons*, Academic Press, New York, 1980, especially Chapter 10; A. H. Schmidt, *Synthesis 1980*, 961; MNDO calculations (J. Macheleid, R. Weiss; Erlangen) also predicted a non-planar structure for **7**.

[8] D. Cremer, E. Kraka, *Croatica Chim. Acta*, in press.

[9] M. Tristani-Kendra, C. J. Eckhardt, J. Bernstein, E. Goldstein, *Chem. Phys. Lett. 98* (1983) 57. A. H. Schmidt, W. Ried, P. Pustoslemsek, W. Schuckmann, *Angew. Chem. 87* (1975) 879; *Angew. Chem. Int. Ed. Engl. 14* (1975) 823; D. G. Farnum, M. A. Neuman, W. T. Suggs Jr., *J. Cryst. Mol. Struct. 4* (1974) 199; H. Dietrich, W. Mahdi, P. H. M. Budzelaar, P. von R. Schleyer, unpublished.

[10] D. Feller, E. R. Davidson, W. T. Borden, *J. Am. Chem. Soc. 104* (1982) 1216.

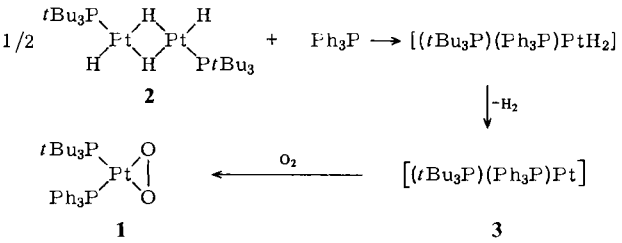
[11] Long bonds are also found in some bridged annulenes: R. Bianchi, T. Pilati, M. Simonetta, *J. Am. Chem. Soc. 103* (1981) 6426; H. B. Bürgi, E. Schefter, J. D. Dunitz, *Tetrahedron 31* (1975) 3089; D. Cremer, B. Dick, *Angew. Chem. 94* (1982) 877; *Angew. Chem. Int. Ed. Engl. 21* (1982) 865; as well as in some homoaromatic cations: D. Cremer, E. Kraka, T. S. Slee, R. F. W. Bader, C. D. H. Lau, T. T. Nguyen-Dang, P. J. MacDougall, *J. Am. Chem. Soc. 105* (1983) 5069. For further examples, see E. Ōsawa, Y. Onuki, K. Mislow, *ibid. 103* (1981) 7475.

Novel Synthesis of an Unsymmetrical $Pt(\eta^2\text{-}O_2)$ Complex

By *Anil B. Goel** and *Sarla Goel*

Studies of the nature of the bonding in $M(\eta^2\text{-}O_2)$ complexes (M = low-valent platinum group metal) and the reactivity of the η^2-dioxygen ligand have received considerable interest[1,2]. To the best of our knowledge, all these systems deal with the symmetrical complexes and no low-symmetry platinum dioxygen complex with dissimilar ligands has ever been reported. Low-symmetry complexes of platinum metals and ligands having different electronic and steric parameters should be useful in studying the *trans*-effect of the ligands, asymmetric synthesis, and homogeneous catalysis[3]. Here, we report the isolation of the first unsymmetrical square-planar $(\eta^2\text{-}O_2)$-platinum complex containing mixed phosphane ligands, $[t\mathrm{Bu_3P}(\mathrm{Ph_3P})\mathrm{Pt}(\eta^2\text{-}O_2)]$ **1**.

Our initial attempts to synthesize unsymmetrical complexes $LL'Pt(\eta^2\text{-}O_2)$ by successive reduction of $PtCl_2(L)(L')$ and reaction with oxygen resulted in excessive decomposition (for sterically less bulky phosphanes, cone angle $\leq 130°$) and gave a mixture of two symmetrical complexes (L_2PtO_2 and L'_2PtO_2). Interestingly, the addition of one equivalent of Ph_3P per Pt atom to a solution of the hydrido-bridged dinuclear platinum complex **2**[4] in benzene resulted in a vigorous reaction with evolution of H_2. The solution, which presumably contained the Pt^0 complex **3**, yielded the desired unsymmetrical complex **1**[5,7] upon exposure to air.



The IR spectrum of **1** shows a medium intensity band at ca. 838 cm^{-1} due to $\nu(O_2)$. The ^{1}H-NMR spectrum (60 MHz, $CDCl_3$, 25 °C) exhibits, in the ratio 9:5, a doublet from the *tert*-butyl groups ($\delta = 1.31$, $J_{PH} = 12.7$ Hz) and two multiplets from the phenyl groups centered at $\delta = 7.38$ (*m*-, *p*-protons) and $\delta = 7.7$ (*o*-protons) in the ratio 3:2). The ^{31}P-NMR spectrum (24 MHz, CH_2Cl_2/C_6D_6, 25 °C) shows two singlets at $\delta = 72.4$ ($t\mathrm{Bu_3P}$) and $\delta = 9.85$ (Ph_3P) with Pt satellites ($K_{Pt,P} = 3940$ and 4443 Hz, respectively), consistent with a *cis*-disposition of the two phosphanes.

$Pt(\eta^2\text{-}O_2)$ complexes are known to react with electrophilic olefins to form the related cycloadducts $L_2PtOOCR_2CR'_2$ via formal Michael addition of a ring-opened platinum peroxide[2a]. However, reaction of complex **1** with electrophilic acetylenes, e.g. dimethyl acetylenedicarboxylate (dma) in benzene, yields the five-membered metallacycle **4**[8] by unique rupture of the O–O bond (supporting evidence—disappearance of IR band at 838 cm^{-1} [$\nu(O_2)$] and appearance of 1580 cm^{-1} band [$\nu(C{=}C)$])[2b].

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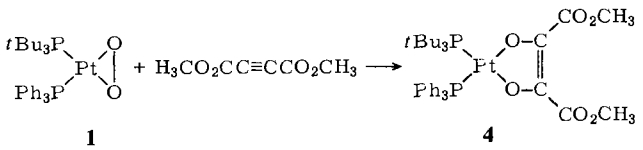

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The ^{1}H-NMR spectrum (60 MHz, $CDCl_3$, 25 °C) exhibits two singlets from the methyl ester groups ($\delta = 3.42$ and 3.70) arising from the nonequivalent methyl groups (different *trans*-effects). Upon hydrolysis with trifluoroacetic acid **4** affords dimethyl dihydroxymaleate in ca. 35% yield. The structure of a diolate complex similar to **4**, obtained by reaction of $[(cyclo\text{-}C_6H_{11})_3P]_2PtO_2$ with dma, has been confirmed by X-ray crystal structure analysis[6].

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CAS Registry numbers:
1, 89378-07-4; **2**, 89378-08-5; **3**, 89378-09-6; **4**, 89378-10-9; $[PtCl(Ph_3Sb)(tBu_2PCMe_2CH_2)]$, 89460-10-6; O_2, 7782-44-7; $H_3CO_2CC{\equiv}CCO_2CH_3$, 762-42-5; dimethyl dihydroxymaleate, 89363-69-9

[1] a) V. J. Choy, C. J. O'Connor, *J. Coord. Chem. Rev. 9* (1972/1973) 145; b) J. S. Valentine, *Chem. Rev. 73* (1973) 235; c) L. Kevan, J. Peone Jr., S. K. Maden, *J. Chem. Educ. 50* (1973) 670; d) G. Henrici-Olivé, S. Olivé, *Angew. Chem. 86* (1974) 1; *Angew. Chem. Int. Ed. Engl. 13* (1974) 29; e) L. Vaska, *Acc. Chem. Res. 9* (1976) 175; f) J. G. Norman, *Inorg. Chem. 16* (1977) 1328; g) S. Sakai, K. Hori, A. Olyoshi, *Inorg. Chem. 17* (1978) 3183; h) Y. Tatsuno, S. Otsuka, *J. Am. Chem. Soc. 103* (1981) 5832.

[2] a) R. A. Sheldon, J. A. VanDoorn, *J. Organometal. Chem. 94* (1975) 115; b) H. C. Clark, A. B. Goel, C. S. Wong, *J. Am. Chem. Soc. 100* (1978) 6241.

[3] a) H. C. Clark, A. B. Goel, C. S. Wong, *J. Organometal. Chem. 190* (1980) C 101; b) A. B. Goel, S. Goel, H. C. Clark, *Synth. React. Inorg. Met. Org. Chem. 11* (1981) 289; c) A. B. Goel, S. Goel, *Inorg. Chim. Acta 59* (1982) 237; d) H. C. Clark, C. Billard, C. S. Wong, *J. Organometal. Chem. 190* (1980) C 105.

[4] The complex **2** was obtained by $NaBH_4$-reduction of the metalated tBu_3P complex $[PtCl(Ph_3Sb)(Bu_2^tPCMe_2CH_2)]$: A. B. Goel, H. C. Clark, unpublished.

[5] IR spectrum showed no ν(Pt–H) band in the 1600–2400 cm^{-1} region.

[6] H. C. Clark, G. Ferguson, A. B. Goel, unpublished.

[7] **3**: *Procedure:* Complex **3** formed in benzene solution was not isolated but exposed to air to afford **1**, which was isolated as a crystalline solid by addition of hexane.

[8] **4**: *Procedure:* Addition of hexane to the reaction solution of complex **1** and dma in benzene or chloroform afforded complex **4**.

Silver-Catalyzed Formation of Crown Ethers; Synthesis and Structure of $[Ag([12]crown\text{-}4)_2][AsF_6]$**

By *Peter G. Jones*, Thomas Gries, Hansjörg Grützmacher, Herbert W. Roesky, Jürgen Schimkowiak,* and *George M. Sheldrick*

Dedicated to Professor Werner Schultheis on the occasion of his 80th birthday

Few isolable complexes of Ag^I with oxygen ligands have been reported[1]. The formation of crown ethers from ethylene oxide in the presence of cations and Lewis acids was known[2], but no crystalline silver complex had been described. We recently succeeded in obtaining the crystalline complex $[(CH_2O)_6Ag_2][Ag][AsF_6]_3$ by reaction of $(CH_2O)_3$ with $AgAsF_6$ and in determining its structure; it contains a macrocyclic $(CH_2O)_6$-ring[3].

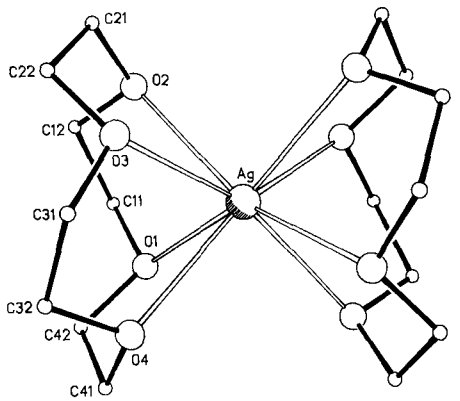

Fig. 1. Structure of the $[Ag([12]crown\text{-}4)_2]^{\oplus}$ cation. Crystal data of the AsF_6 salt: space group $C2$, $a = 1047.1(3)$, $b = 1153.9(3)$, $c = 980.1(3)$ pm, $\beta = 91.83(3)°$, $Z = 2$, $R = 0.070$ for 1854 absorption-corrected reflections with $F > 4\sigma(F)$. Silver and arsenic atoms lie on the twofold axes 0, y, $\frac{1}{2}$ and 0, y, 0 respectively. The average Ag–O bond length is 257 pm. The structure determination was made more difficult by the fact that the positions of the Ag, As, and F atoms all correspond to the centrosymmetric space group $C2/m$. Further details of the crystal structure can be obtained from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, on quoting the deposition number CSD 50760, the names of the authors, and the journal citation.

We have now found that reaction of $AgAsF_6$ with ethylene oxide in liquid SO_2 leads to a crystalline complex of composition $[Ag(OCH_2CH_2)_8][AsF_6]$ **1**[4]. The crystal structure analysis of **1** (Fig. 1) shows a "sandwich" structure with eight-coordinated Ag^I. The coordination geometry at silver corresponds to that of a cube, two opposite faces of which are rotated through ca. 30°. (A 45° rotation would give rise to an Archimedean antiprism.) The ligands are two molecules of 1,4,7,10-tetraoxacyclododecane ([12]crown-4)[5] with non-crystallographic C_4 symmetry (torsion angles g^+g^+a in the O–C–C–O moieties[6]). This conformation is known for other complexes of [12]crown-4[6].

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CAS Registry numbers:
1, 89773-89-7; $AgAsF_6$, 12005-82-2; ethylene oxide, 75-21-8.

[1] F. A. Cotton, G. Wilkinson, *Advanced Inorganic Chemistry*, Wiley, New York 1980.

[2] J. Dale, K. Daasvatn, *J. Chem. Soc. Chem. Commun. 1976*, 295.

[3] H. W. Roesky, E. Peymann, J. Schimkowiak, M. Noltemeyer, W. Pinkert, G. M. Sheldrick, *J. Chem. Soc. Chem. Commun. 1983*, 981.

[4] *Experimental:* 5.13 g of ethylene oxide and then 30 ml SO_2 as solvent are condensed into one limb of a Schlenk apparatus containing 1.73 g $AgAsF_6$. The apparatus is closed with Teflon valves so that the reaction mixture may be warmed carefully to room temperature while stirring. Light is excluded. CAUTION! The apparatus is under pressure; all operations must be carried out in a fume cupboard behind a protective screen. After 20 h the precipitate is allowed to settle and the colorless clear solution decanted off. After removal of the SO_2 by condensation a colorless crystalline solid and a black liquid remain. The liquid is pipetted off and the residue dried *in vacuo* and then recrystallized from SO_2. Yield 25% **1** decomp. pt. 120 °C. The liquid is mostly 1,4-dioxane.

[5] Main IR bands of **1**: (KBr/Nujol): 1365 m, 1350 w, 1305 m, 1293 m, 1250 m, 1238 sh, 1135 s, 1095 s, 1021 s, 915 s, 845 s, 698 s, 550 w, 398 s cm^{-1}. **1** fluoresces in the Raman spectrum.

[6] J. Dale, *Isr. J. Chem. 20* (1980) 3, and references cited therein.

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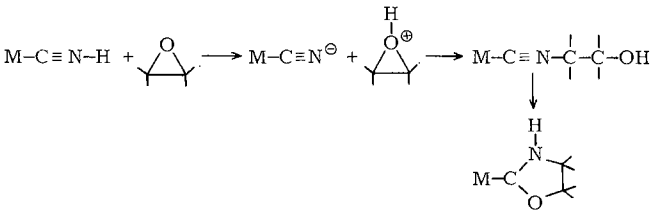
Reactions of the Cyanometal Acids $H_4M(CN)_6$ (M = Fe, Ru, Os), $H_2Pt(CN)_4$, and $HAu(CN)_2$ with Epoxides: β-Hydroxyalkyl Isocyanide- and Oxazolidine-2-ylide-Metal Complexes**

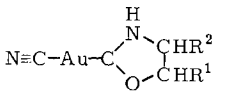
By *Wolfgang Beck**, *Wolfgang Weigand, Ulrich Nagel,* and *Matthias Schaal*

"Cyanometal acids" such as $H_4Fe(CN)_6$ are classical complexes in which isohydrocyanic acid, the parent compound of the isocyanides, is stabilized as a ligand at the metal atom (M–C≡N–H). In the solid state these compounds contain hydrogen bonds of the type M–C≡N–H...N≡C–M[1]. As early as 1901, *von Baeyer* and *Villiger*[2] investigated the reaction of $H_4Fe(CN)_6$ with ethylene oxide in connection with studies of the "basic properties of oxygen". The ice-like product obtained was initially held to be a hydrate of ethylene oxide, and its more precise characterization was postponed until a "cooler time of the year"[2].



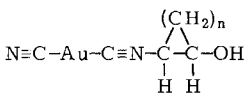
Since the reaction of $H_4Fe(CN)_6$ with α,β-unsaturated carbonyl compounds leads to novel γ-oxoisocyanide complexes[3], we were interested in the reaction of cyanometal acids with electrophiles. We have now found that with epoxides under heterogeneous conditions (in $CHCl_3$), metal complexes are formed with β-hydroxyalkyl isocyanide- or oxazolidine-2-ylide ligands. Ring cleavage is effected by attack of the nucleophilic N atom of a cyano group at the *O*-protonated oxirane[4].

In this way, the carbene complexes **1a** or **1b** are formed from $HAu(CN)_2$ and propene oxide or styrene oxide.



1a: R^1 = Me, R^2 = H
1b: R^1 = H, R^2 = Ph

In contrast, reaction with cyclopentene and cyclohexene oxides affords complexes **2a** and **2b**, respectively, with open-chain β-hydroxyalkyl isocyanide ligands. Ring opening proceeds *trans*-diaxially in these bicyclic epoxides[5], and hence with **2a**, **b** precludes ring closure to the oxazolidine derivatives.



2a: n = 3
2b: n = 4

Fehlhammer et al. obtained a series of complexes with ligands such as in **1** and **2** directly from β-hydroxyalkyl isocyanides and metal compounds[6]. Complexes of the type XAu(carbene) have been isolated using other routes, as described by *Bonati* et al. as well as by *Fischer* et al.[7]. The structures of **1** and **2** have been corroborated by spectroscopic data (Table 1 and 2).

Table 1. Characteristic IR bands [cm^{-1}] for complexes **1**–**3** (in KBr).

1a:	3030 s, br (NH, CH) [a]; 2155 s (C≡N); 1560 s, 1190 s (N=C=O)
1b:	3000 s, br (NH, CH) [a]; 2160 s (C≡N); 1560 s, 1175 s (N=C=O)
2a:	3340 s, br (OH); 2960, 2875 m (CH); 2260 s (C≡N–R); 2165 m (C≡N); 1090 m (C–O)
2b:	3330 s (OH); 2950, 2860 m (CH); 2260 s (C≡N–R); 2165 s (C≡N); 1085 s (C–O)
3a:	3200 s, br (NH, CH) [a]; 2130 s (C≡N); 1550 s, 1175 m (N=C=O)
3b:	3100 s, br (NH, CH) [a]; 2240 s, 2130 s (C≡N); 1540 s, 1170 s (N=C=O)

[a] Structured.

Table 2. 90 MHz ^{1}H-NMR data of complexes **1**–**2** (δ-values, TMS int.).

1a [a]:	1.18–1.40 (m, 3H, Me), 4.11–5.15 (m, 3H), 11.42–11.74 (m, 1H, NH)
1b [a]:	4.44 [c], 5.28 [c] (dd, ^2J = 7.4 Hz, 2H), 4.98 [c] (dd, ^3J = 9.3 Hz, 1H), 7.25–7.50 (m, 5H, Ph), 12.08 (s, 1H, NH)
2a [b]:	1.64–2.29 (m, 6H, $(CH_2)_3$), 4.08 [c] (m, 1H, C≡N–C*H*), 4.56 [c] (m, 1H, HO–C*H*), 4.90 [c] (d, 1H, OH)
2b [a]:	1.18–2.22 (m, 8H, $(CH_2)_4$), 3.57–3.96 (m, 2H, C≡N–C*H*, HO–C*H*), 5.62 (s, 1H, OH)

[a] In $[D_6]$dimethyl sulfoxide. [b] Solvent $CDCl_3$. [c] Centered.

The result of the X-ray structure analysis of **1b** is shown in Figure 1. The distances Au–$C_{carbene}$, C–N, and C–O are in good agreement with those of similar complexes[8].

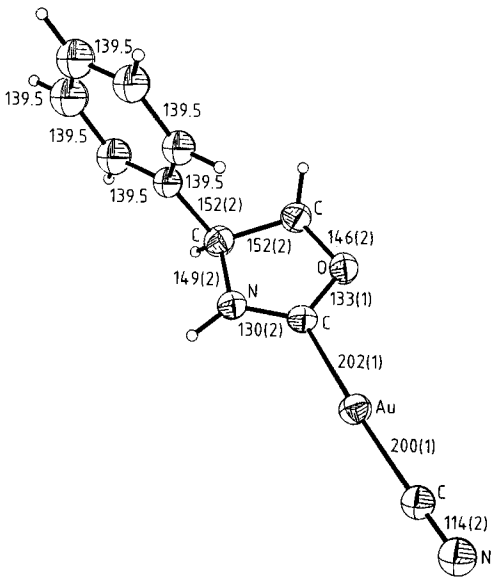


Fig. 1. Molecular structure of the 1,3-oxazolidine-2-ylide gold complex **1b** in the crystal (the thermal ellipsoids correspond to 20% residence probability) with atomic distances [pm]. The phenyl substituent was treated as a regular hexagon, and the hydrogen atoms inserted in the positions calculated. Space group $P2_1/c$, a = 826.9(5), b = 1316(1), c = 1023.8(7) pm, β = 103.02(5)°, Z = 4; 1762 reflections ($I > 2\sigma(I)$), 77 parameters (measurements: Nicolet P3, solution SHELXTL), R_1 = 0.062. Further details of the crystal structure investigation can be obtained from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, by quoting the depository number CSD 50770, the names of the authors, and the journal citation.

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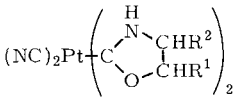
[**] Pseudohalometal compounds, Part 63. This work was supported by the Fonds der Chemischen Industrie as well as by Bayer AG, Leverkusen, BASF AG, Ludwigshafen, Hoechst AG, Gendorf, and Chemische Werke Hüls, Marl.—Part 62: W. Beck, H. Nöth, *Chem. Ber. 117* (1984) 419.

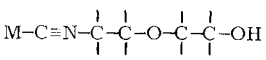
The 1,3-oxazolidine ring is completely planar (±1 pm) and the Au atom is only 13 pm above this plane, i.e. the carbene C atom has practically a trigonal-planar environment.



3a: R^1 = Me, R^2 = H
3b: R^1 = H, R^2 = Ph

The bis(carbene) complexes **3a** and **3b** were synthesized from $H_2Pt(CN)_4$ and propene or styrene oxides, respectively. In the IR spectrum (Table 1), **3a** exhibits one ν(CN) band and **3b** two ν(CN) bands corresponding to the *trans*- and *cis*-configurations, respectively.

The reactions of epoxides with the hexacyanometal acids $H_4M(CN)_6$ of iron, ruthenium, and osmium are more complex. As indicated by HPLC analysis [reversed phase C_{18} column, eluent EtOH/H_2O (7:3), UV detection (λ = 260 nm)], a mixture of at least seven complexes with similar product distribution for the Fe^{II}, Ru^{II}, and Os^{II} compounds is formed in reactions with styrene oxide. Elemental analysis indicates that 1.2—1.5 ethylene oxide moieties are added on average per CNH moiety, i.e. oligo(ethylene glycol) groups such as



also form at the isocyanide ligand.

In the mass spectrum of the iron complex obtained with styrene oxide, $[FeCNCH(Ph)CH_2O]^{\oplus}$ appears as the ion with the highest mass (*m/z* 202) [IR (KBr); 3280 br, ν(OH); 2150, ν(CNR); 2085 cm^{-1}, ν(CN)].

The reactions described here of the MCNH group with epoxides to afford carbene complexes are comparable to those of carbonylmetal compounds with three-membered heterocycles (epoxides, aziridine), which also lead to cyclic carbene ligands[9]. However, in the latter case, nucleophilic attack of the hetero-ring atom at the carbonyl carbon atom has been postulated.

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[5] H. B. Kagan: *Organic Stereochemistry*, Thieme, Stuttgart 1977, p. 165.
[6] K. Bartel, W. P. Fehlhammer, *Angew. Chem. 86* (1974) 588; *Angew. Chem. Int. Ed. Engl. 13* (1974) 600; W. P. Fehlhammer, Habilitationsschrift, Universität München 1976.—In the reaction of $(OC)_5WCNSiMe_3$ with 2,2-dimethyloxirane, $(OC)_5WCN-CH_2CMe_2OH$ was obtained after hydrolysis (W. P. Fehlhammer, F. Beck, unpublished).
[7] F. Bonati, G. Minghetti, *J. Organomet. Chem. 59* (1973) 403; E. O. Fischer, R. Aumann, *Chem. Ber. 114* (1981) 1853.
[8] K. H. Dötz, H. Fischer, P. Hofmann, F. R. Kreissl, U. Schubert, K. Weiss: *Transition Metal Carbene Complexes*, Verlag Chemie, Weinheim 1983.
[9] M. M. Singh, R. Angelici, *Angew. Chem. 95* (1983) 160; *Angew. Chem. Int. Ed. Engl. 22* (1983) 163; *Angew. Chem. Suppl. 1983*, 184.

$[Cu_5I_7]^{2\ominus}$—An Isopolyanion with Cyclic Face-to-Face Linking of CuI_4 Tetrahedra**

By *Hans Hartl** and *Farbod Mahdjour-Hassan-Abadi*

In our studies on iodocuprates(I) $R_mCu_nI_p$ with various organic cations $R^{\oplus}$ we demonstrated the existence of a series of unusual polyanions[1a,b]. Further investigations with tetra-*n*-propylammonium as cation have now revealed the existence not only of a binuclear planar anion $[Cu_2I_4]^{2\ominus}$[1c] and a polymeric chain-like anion $^1_\infty[Cu_3I_4]^{\ominus}$[1b] but also of an oligomeric anion $[Cu_5I_7]^{2\ominus}$ with a fascinating structure: seven $I^{\ominus}$ ions form a pentagonal bipyramid with only slight deviations from C_{5h} symmetry; the five face-to-face linked iodide tetrahedra of the pentagonal bipyramid contain Cu^I ions (cf. Fig. 1).

Following the successful synthesis of $R^1_\infty[Cu_2I_3]$ (R = $[(C_2H_5)_4N]^{\oplus}$ or $[(CH_3)_2N{=}CH{-}N{=}CH{-}N(CH_3)_2]^{\oplus}$)[1a] and $[(C_3H_7)_4N]^1_\infty[Cu_3I_4]$[1b] with unusual face-to-face linking of two and three CuI_4 tetrahedra, respectively, an iodocuprate(I) with five cyclic condensed CuI_4 tetrahedra could be isolated in $[(C_3H_7)_4N]_2[Cu_5I_7]$ **1**[2].

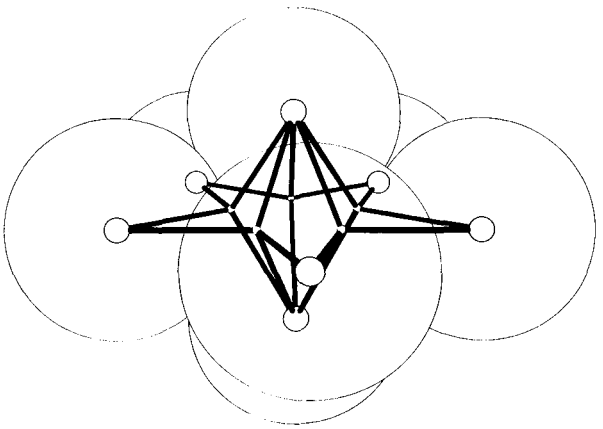

Fig. 1. Structure of the $[Cu_5I_7]^{2\ominus}$ anion in the crystal of **1** (idealized).

A pentagonal bipyramid can be regarded as a section of a centered icosahedron and is a structural unit which frequently occurs in the $AgI/I^{\ominus}$ system[3], but which has also been found in a halocuprate(I), $[pyH]_2[Cu_5Br_7]$[4]. In this compound, however, the pentagonal bipyramids of $Br^{\ominus}$ ions are not isolated, but are linked together edge-to-edge in a three-dimensional arrangement. As a result, additional tetrahedral cavities are formed; the Cu^I ions are statistically distributed with different population parameters over the greater number of tetrahedral cavities. $[pyH]_2{}^3_\infty[Cu_5Br_7]$ is a solid state ion-conductor. In contrast, only five tetrahedral vacancies are available for the five Cu^I ions in **1**. The Cu atoms are not located exactly in the centers of the tetrahedra, since this arrangement would lead to extraordinarily short distances d_{Cu-Cu} = 0.41 × length of tetrahedron edge ≈ 185 pm[5]; they are therefore dislocated in the direction of a tetrahedron face, above or below the plane of the

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[**] Synthesis and Structural Investigation of Iodocuprates(I), Part 4.—Part 3: [1b].

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I_5 ring. The temperature factors of the Cu atoms showed unusually large coefficients for the direction perpendicular to the plane of the I_5 ring; this anisotropy disappeared on refinement of the Cu positions as split atom sites. The alternative population of two crystallographically independent positions within each of the CuI_4 tetrahedra is possible. In three tetrahedra these two possible positions have a distance of approx. 68 pm, in the remaining two tetrahedra a distance of approx. 96 pm (Fig. 2). An alternating distribution of the Cu^I ions at positions above or below the I_5 ring is impossible because of the uneven number of ring members; the arrangement shown in Figure 2 leads to plausible Cu–Cu distances (mean value 258 pm). Each Cu atom shows three short and one longer Cu–I distances. The distances from the Cu atoms to the I atoms of the I_5 ring vary between 251(2) and 257(2) pm (mean value 253 pm), those to the I atoms at the apices of the pyramids between 264(2) and 277(2) pm (mean value 270 pm) and between 314(2) and 342(2) pm (mean value 325 pm), respectively. The intramolecular I–I distances of 416.7(2) between the apices of the pyramids are distinctly shorter than the remaining I–I distances, which vary between 435.8 and 459.3(2) pm (mean value 445 pm).

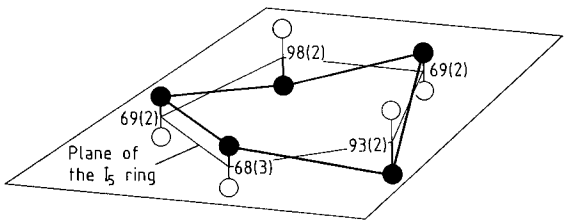

Fig. 2. Distribution of the Cu atoms of the $[Cu_5I_7]^{2\ominus}$ anion over the ten possible split atom positions [6]. The split atoms are located above or below the plane of the I_5 ring. The numerical values indicate the distance between the two possible Cu positions within the respective I tetrahedra; the alternative arrangements—black and white spheres, respectively—enable Cu···Cu contacts of 257–263 pm (mean value 259 pm) and 247–262 pm (mean value 257 pm).

A ring-shaped coupling of five MX_4 tetrahedra in a plane is also found in compounds containing the $^1_\infty[Ag_5I_6]^\ominus$ anion[3a,b]; but here the tetrahedra are linked edge-to-edge, and the rings are additionally linked via common tetrahedron corners to give a column-like structure. A face-to-face linkage of AgI_4 tetrahedra in analogy to $[Cu_5I_7]^{2\ominus}$ is not to be expected for steric reasons ($r(Ag^\oplus) > rCu^\oplus$))[5].

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CAS Registry number:
1, 89746-86-1

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[2] *Procedure:* A mixture of $[Pr_4N]I$ (2 g, 6.4 mmol), I_2 (1.62 g, 6.4 mmol) and Cu powder (1.59 g, 25 mmol) in anhydrous acetone (70 mL) is heated under reflux until a pale yellow solution is obtained. After hot filtration and cooling (about 2 d, about 5 °C), yellowish white crystals of the composition $[Pr_4N][Cu_3I_4]$ precipitate (m.p. 210–211 °C). After renewed filtration and addition of ether, small amounts of needle-shaped crystals of composition $[Pr_4N]_2[Cu_5I_7]$ (m.p. 207–210 °C) can be separated from the main product $[Pr_4N]_2[Cu_2I_4]$ (m.p. 168–169 °C) of the precipitate (white crystals) by shaking in a mixture of diiodomethane/toluene of appropriate density.

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[5] A. F. Wells: *Structural Inorganic Chemistry*, 4th edit., Clarendon Press, Oxford 1975, p. 158.

[6] Monoclinic crystals, $P2_1/c$, $a = 1223.0(5)$, $b = 1254.3(5)$, $c = 3303.1(9)$ pm, $\beta = 115.04(5)°$, $Z = 4$, $\rho_{calc} = 2.29$ g cm^{-3}; $R = 0.065$, $R_w = 0.061$ ($Cu_{K\alpha}$, $\lambda = 1.5418$ Å, 6798 reflections, 4536 with $I > 2\sigma(I)$, absorption and extinction correction, $\mu = 405$ cm^{-1}, anisotropic temperature factors, no H atom positions, 390 refined parameters). Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD 50777, the names of the authors, and the journal citation.

As_4tBu_2—The First Bicyclo[1.1.0]tetraarsane**

By *Marianne Baudler** and *Stefan Wietfeldt-Haltenhoff*

Small-ring compounds have played a major role in preparative nonmetal chemistry for many years. Following the synthesis of the monocyclic arsenic three-membered ring compound $(AstBu)_3$[1] and the bicyclo[3.3.0]octaarsane As_8tBu_6[2], the question arose as to whether also organoarsanes with a bicyclic skeleton of two annelated three-membered rings are capable of existence and whether or not they are isolable. Such compounds would be formally regarded as primary cleavage products of the As_4 tetrahedron. We have now succeeded in synthesizing 2,4-di-*tert*-butylbicyclo[1.1.0]tetraarsane **1**, the first compound with an $As_4(2)$ ring skeleton.

1 is formed in the dehalogenation of a mixture of *tert*-butyl(dichloro)arsane and arsenic(III) chloride with lithium hydride below 0 °C:

$$2\,tBuAsCl_2 + 2\,AsCl_3 + 10\,LiH \longrightarrow \underset{\mathbf{1}}{As_4tBu_2} + 10\,LiCl + 5\,H_2$$

Other products formed in the reaction include monocyclic and chain-shaped *tert*-butylarsanes and, above 0 °C, increasingly polycycles with higher arsenic content. The product pattern is strongly dependent upon the reaction conditions (solvent, temperature, molar ratio and concentration of the reactants, and reaction rate). Under suitable reaction conditions (optimized by ^{1}H-NMR spectroscopic monitoring), **1** can be obtained free of arsenic-containing by-products and, by work-up at low temperature, can be isolated in analytically pure form[3].

At −40 °C, **1** is a reddish-orange to dark-red, moldy smelling solid which is stable in the absence of air and light at −196 °C. It is readily soluble in tetrahydrofuran and in aliphatic and aromatic hydrocarbons; at −78 °C, the solutions slowly undergo decomposition. At room temperature, or when exposed to light, **1** disproportionates to arsenic metal, $(AstBu)_4$, and other *tert*-butylarsanes. **1** is only slightly sensitive to hydrolysis, but extremely sensitive to oxidation. Its composition is confirmed by correct elemental analysis and the mass spectrum (10 eV, 180 °C), in which M^+ (m/z 414) as base peak and a signal group with highest mass numbers are observed. The IR spectrum, un-

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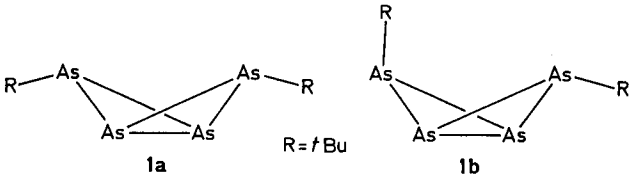
like those of other *tert*-butylarsanes, shows three bands at 400 (s), 371 (s), and 299 (m) cm^{-1}.



1a **1b**

The constitution of **1** follows from the ^{1}H-NMR spectrum ([D$_6$]benzene, 24°C), which shows a singlet at $\delta = 0.91$ for the *tert*-butyl groups. The strong shielding of the ^{1}H-nuclei, which is even greater than in (As*t*Bu)$_3$ ($\delta = 1.16$, 1.41[1]), proves the presence of the highly strained bicyclo[1.1.0]tetraarsane system. Also consistent with the presence of the bicyclo[1.1.0]tetraarsane system are the high- and low-field positions of the singlets for the primary and tertiary C atoms in the ^{13}C{^{1}H}-NMR spectrum ([D$_6$]benzene, 24°C) at $\delta = 23.48$ and 44.03, respectively, which have previously never been observed in the case of a *tert*-butylarsane. Since the NMR spectroscopic findings reveal that the two *tert*-butyl groups are equivalent, it follows that the sterically more favorable *exo/exo*-isomer **1a** (symmetry C_{2v}) is present[4]. Probably, the *endo/exo*-isomer **1b** is also formed initially, but already decomposes under the reaction conditions.

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1a, 89828-42-2; **1b**, 89887-42-3.

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[3] *Procedure:* A solution of *tert*-butyl(dichloro)arsane (9.18 g, 45.2 mmol) and arsenic(III) chloride (8.64 g, 47.7 mmol) in tetrahydrofuran (THF) (60 mL) is cooled to −35°C and added dropwise with vigorous stirring within 4–4.5 h at −35°C to a suspension of lithium hydride (1.96 g, 247 mmol) in THF (60 mL). The mixture is stirred for a further 15 min, rapidly filtered at −35°C, and the solvent removed from the filtrate as quickly as possible in vacuo ($< 10^{-2}$ torr) at the same temperature. The orange-yellow solid residue is treated with 500 mL *n*-pentane and the mixture stirred for 3 h at −78°C. After filtration at −40°C, the residue is washed three times with 20 mL cold pentane, the filtrates are combined, and the solvent is removed at −40°C; yield 4.8 g **1** (51% referred to *t*BuAsCl$_2$), purity 100% (^{1}H-NMR). All operations must be carried out in the absence of air and light.

[4] In principle, the *endo/endo*-isomer would also appear possible, but according to model considerations this can be ruled out.

Synthesis of *N*-(Arylmethylene)dehydroalanine Esters**

By *Günter Wulff** and *Helmut Böhnke*

Dehydroamino acids play an important role in nature[1]. For example, in the biosynthesis of some amino acids, *N*-pyridoxylidenedehydroalanine is formulated as a reactive intermediate which undergoes Michael additions with nucleophiles. By analogy, *N*-(arylmethylene)dehydroalanine esters could serve as a valuable equivalent for the synthon $^{\oplus}CH_2-CH(NH)_2-COOH$ in a biomimetic synthesis of α-amino acids.

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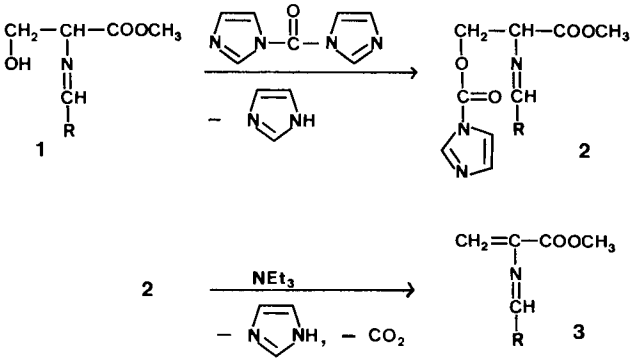
[**] This work was supported by the Fonds der Chemischen Industrie.

Whereas *N*-(arylmethylene)dehydroamino acid esters substituted at the CC double bond are known and are stable[2,3], the preparatively interesting, highly reactive parent compounds (e.g. the *N*-benzylidenedehydroalanine methyl ester **3a**) have previously only been detected in solution by ^{1}H-NMR spectroscopy[3].



a, R = C_6H_5; **b**, R = 4-(C_6H_5)C_6H_4

Using a very straightforward route, we have now succeeded in preparing and characterizing the reactive compounds **3a** and **3b**[4]. **3** was synthesized from the Schiff base of the serine methyl ester **1**[5] by modifying a recently published method[6]: the urethane **2**—detected by ^{1}H-NMR spectroscopy—obtained from **1** and *N,N'*-carbonyldiimidazole—reacts quantitatively (NMR spectroscopy) with triethylamine in a few minutes at room temperature to afford the dehydro compound **3**. After separation of imidazole, **3a** and **3b** can be obtained by crystallization at lower temperature; however, they could be further directly reacted in solution[7].

Whereas upon warming to room temperature **3a** decomposes to a colorless, viscous liquid, **3b** is a white, crystalline solid which can be manipulated at room temperature and can be stored in a refrigerator for some time under an inert gas atmosphere. Compound **3b** is therefore suitable for further studies of the properties of *N*-(arylmethylene)dehydroalanine esters. Under the same experimental conditions, **3b** adds diethylamine ten times faster than the more stable *N*-acetyldehydroalanine methyl ester[8]. A further increase in reactivity can be achieved by introducing substituents into the aryl group[9]. An additional advantage of using compounds of type **3** is that the protecting group for the amine function can readily be removed, e.g. by an equimolar amount of HCl in water/diethyl ether at room temperature.

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1a, 40216-75-9; **1b**, 89891-08-7; **2a**, 89891-09-8; **2b**, 89891-10-1; **3a**, 70361-62-5; **3b**, 89891-11-2; *N,N'*-carbonyldiimidazole, 530-62-1.

[1] Recent reviews: C. H. Stammer, *Chem. Biochem. Amino Acids Pept. Proteins 6* (1982) 33; E. Gross, *Adv. Exp. Med. Biol. 86B* (1977) 131; U. Schmidt, J. Häusler, E. Öhler, H. Poisel, *Prog. Chem. Org. Nat. Prod. 37* (1979) 251; H. G. Floss, J. C. Vederas in C. Tamm: *New Comprehensive Biochemistry, Vol. 3: Stereochemistry*, Elsevier, Amsterdam 1982, p. 161.

[2] For example: E. Öhler, E. Prantz, U. Schmidt, *Chem. Ber. 111* (1978) 1058.

[3] E. Öhler, U. Schmidt, *Chem. Ber. 112* (1979) 107.

[4] The ^{1}H-NMR spectrum of **3a** is consistent with that described in [3]. The structure of **3b** was determined by ^{1}H-NMR and mass spectroscopy as well as by elemental analysis.

[5] **1a** was prepared using the method described by J. W. Davis, US-Pat. 3718688 (1973); **1b** was prepared analogously. The structures were determined by ^{1}H- and ^{13}C-NMR spectroscopy as well as by elemental analysis. Although racemic serine can, in principle, also be used L-serine was used on grounds of cost.

[6] R. Andruszkiewicz, A. Czerwiński, *Synthesis 1982*, 986.

[7] *Experimental procedure* using the example of **3b**: **1b** (560 mg, 2.0 mmol) [5] and an equimolar amount of *N,N'*-carbonyldiimidazole were dissolved in 10 mL anhydrous diethyl ether and 2 mL anhydrous tetrahydrofuran under N_2. After addition of 1 mL triethylamine, the mixture was stired for 2–3 min at room temperature, 50 mL cold *n*-pentane added, and the resulting mixture cooled for 30 min at −15 °C and filtered at this temperature. **3b** crystallizes at −90 °C; yield: 325 mg (62%); m.p. (in sealed ampule) = 60–61 °C (decomp.).

[8] E. Rothstein, *J. Chem. Soc. 1949*, 1968.

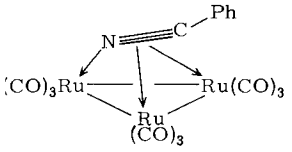
[9] Attempts to prepare the *N*-salicylidenedehydroalanine methyl ester indicated that this is considerably more reactive than **3a**.

Stepwise Hydrogenation of Benzonitrile on a Ru_3-Cluster**

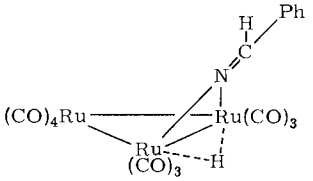
By *Wolfgang Bernhardt* and *Heinrich Vahrenkamp**

Nitriles can be reduced to amines by H_2 under pressure using metal catalysts, e.g. Raney nickel. Single steps of this reaction have been studied in an exemplary way for Fe_3-clusters[1]. Here, we report other part-steps which occur on Ru_3-clusters.

With the aim of obtaining the μ_3-η^2-benzonitrile complex **1**, we passed H_2 into a mixture of $Ru_3(CO)_{12}$ and PhCN in ligroin for 30 min at 130 °C using the conditions described by *Keller* et al.[2] for the corresponding Fe_3-complex[1]. However, instead of **1** we isolated the orange-yellow μ_2-η^1-complex **2** in 41% yield after chromatography on silica gel[3].



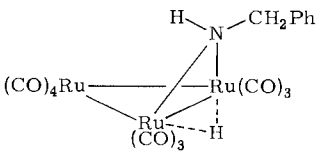
1



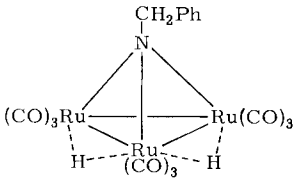
2

The CN-containing ligand in **2** is derived from benzylideneamine, the initial product of hydrogenation of benzonitrile. For this reaction to occur under the very mild hydrogenation conditions, coordination of the substrate to the cluster is a prerequisite. Whether complex **2** is formed from a precursor related to **1** is not yet clear. The constitution of **2** is determined by crystal structure analysis[4]. The C=N bond length in **2** (127 pm) is in the double bond region; the C≡N bond in benzonitrile is 13 pm shorter[5]. All the atoms of the benzylidenamino ligand and the two bridged ruthenium atoms are coplanar, and this plane forms an angle of 109° with the Ru_3 plane.

Further hydrogenation of **2** should afford the recently described **3**[6]. However, renewed reaction of **2** with H_2 as described above gave 49% of the orange-yellow μ_3-η^1-complex **4** after 90 min. The composition of **4** results from elemental analyses and the EI mass spectrum, and its structure can be deduced from the relationship between its spectra[3] and those of other $H_2Ru_3(CO)_9(\mu_3\text{-}X)$ complexes[7]. **4** is the product of oxidative addition of the NH moiety of the benzylamino ligand in **3** to the free ruthenium atom, resulting in CO elimination. The assumption that **3** is an intermediate on the route from **2** to **4** is corroborated in that under the chosen reaction conditions pure **3**[6] is converted into **4**.



3



4

The bonding and activation of the substrate by several metal atoms in these complexes is an example for the cluster-surface analogy. In contrast to the Fe_3/nitrile system[1], in which the key steps occur on μ_3-bonded, CN-containing ligands, the present case demonstrates that complete hydrogenation of the CN bond at atmospheric pressure is possible with coordination involving only the nitrogen and two metal atoms. We are presently attempting to obtain the precursor complex of **2** containing unaltered benzonitrile and to find a method of cleaving the benzylamine from **4**.

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[1] M. A. Andrews, H. D. Kaesz, *J. Am. Chem. Soc. 101* (1979) 7238, 7255.

[2] E. Keller, D. Wolters, *Chem. Ber. 117* (1984) 1572.

[3] ^{1}H-NMR data ($CDCl_3$, int. TMS) for **2**: δ = 9.05 (NCH), 7.58 (Ph, m), −13.30 (Ru_2H); **4**: δ = 7.33 (Ph, m), 5.04 (CH_2), −17.13 (Ru_2H). – IR data (C_6H_{12}, cm^{-1}) for **2**: 2097 w, 2061 vs, 2051 s, 2020 s, 1997 sh, 2003 m, 1985 w, 1965 vw, 1952 vw; **4**: 2111 m, 2078 s, 2052 vs, 2042 sh, 2028 w, 2010 s, 1992 s, 1980 m.

[4] Monoclinic, $P2_1$, a = 960.5(2), b = 929.4(2), c = 1306.0(3) pm, β = 111.23(2)°, Z = 2, 2463 reflections, R = 0.031. Further details on the crystal structure investigation can be obtained from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, by quoting the depository number CSD 50674, the names of the authors and the journal citation.

[5] G. Fauvet, M. Massaux, R. Chevalier, *Acta Crystallogr. B34* (1978) 1376.

[6] P. M. Lausarot, G. A. Vaglio, M. Valle, A. Tiripicchio, M. Tiripicchio-Camellini, *J. Chem. Soc. Chem. Commun. 1983*, 1391.

[7] E. Sappa, O. Gambino, G. Cetini, *J. Organomet. Chem. 35* (1972) 375; E. Sappa, L. Milone, *ibid. 61* (1973) 383.

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Dialkylboryl-Substituted Triphenylphosphonium Ylides

By *Hans-Jürgen Bestmann** and *Thomas Arenz*

The hydrogen atom in triphenylphosphonium ylides of type **1** can be exchanged[2,3] via transylidation by reactions with halogen compounds in the molar ratio 2 : 1[1]. So far these reactions have only been carried out with halides of elements of the 4th–7th main groups of the Periodic System[2,3].

It can be expected that ylides in which an element of the 1st to 3rd main groups is bonded to carbon are more stable

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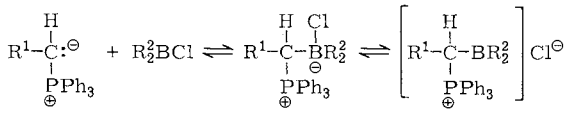
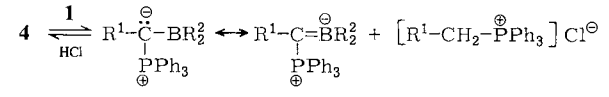
than **1**. We therefore examined reactions of the readily accessible dialkylchloroboranes **2**[4] with phosphoranes **1**[5].



1 **2** **3** **4**



5A **5B** **6**

In boiling benzene the reaction proceeds as expected with transylidation and formation of the α-dialkylboryl-substituted triphenylphosphonium ylides **5**[6] (Table 1) and the phosphonium salts **6**, which precipitate from the solution. We assume that the adduct **3** is initially formed[7] and is subsequently converted into **4**. The products **5** and **6** are obtained by reaction of **1** with **3** as well as **4**.

Table 1. Dialkylboryl-substituted triphenylphosphonium ylides **5** by reaction of **1** with **2** in the molar ratio 2:1. NMR: δ-values, $\nu_{1/2}$ = line width in the ^{11}B-NMR spectrum.

	R^1	R^2	Yield [%]	NMR ^{31}P [a]	NMR ^{11}B	$\nu_{1/2}$ [Hz]	MS Int. [%] [g] M^+-1	M^+	M^++1
a	CH_3	*c*-C_5H_9[b]	65	+26.2	+56[d]	436	22	100	29
b	C_2H_5	*c*-C_5H_9[b]	85	+27.0	+55[e]	402	24	100	30
c	CH_3	*n*-C_5H_{11}	88	+24.2	+54[d]	344	23	100	25
d	C_6H_5	*n*-C_5H_{11}	76	+19.2	+52[e]	384	22.5	100	35
e	C_6H_5	*c*-C_5H_9[b]	71	+20.6	+58[e]	360	24	100	37
f	C_6H_5	*c*-C_6H_{11}[c]	70	+20.7	+51[d]	[f]	21.5	100	39.5

[a] In C_6D_6, H_3PO_4 as external standard. [b] Cyclopentyl. [c] Cyclohexyl. [d] In C_6D_6 at RT; Et_2O-BF_3 as external standard. [e] In [D_8]toluene, 80°C, Et_2O-BF_3 as external standard. [f] Extremely flat bands. [g] Intensity in molecular ion region.

The new ylides, which can be described in terms of the mesomeric formulations **5A** ↔ **5B**, are crystalline compounds which decompose without melting sharply over a wide temperature interval on heating. The ^{1}H-NMR data of **5** are consistent with expectation. In the ^{13}C-NMR spectrum the absorption of the C atoms directly bonded to boron is characterized by strong line-broadening. The ^{11}B-NMR spectrum shows a broad signal in the region $\delta = 50$ (diethyl ether/trifluoroborane as external standard), whereas trialkylboranes absorb at $\delta = 80$. The ^{31}P-NMR signal appears at $\delta = +20$ to $+27$ (H_3PO_4 as external standard) and is thus shifted downfield into the resonance region of stabilized phosphonium ylides compared to that of the ylide **1**. We ascribe the upfield shift of the ^{11}B-NMR signals compared to those of trialkylboranes and the downfield shift of the ^{31}P-NMR signals compared to those of the phosphorane **1** to participation of the mesomeric form **5B** with partial B=C double bonding.

When anhydrous hydrogen chloride is passed into a solution of **5** in ether or tetrahydrofuran the title compounds decompose to the starting compounds **1** and **2**. **3** is formed on addition of HCl, but it cannot be established whether the phosphonium chloride **4** occurs as intermediate. **3** decomposes in an equilibrium reaction into **2** and **1**. Compound **1** reacts with further HCl to give the phosphonium salt **6** and is thus removed from the equilibrium. The chloroborane **2** formed in the reaction was detected by reaction with methanol and subsequent conversion of the dialkyl borinate into the ketone[8].

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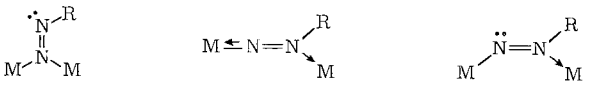
[1] H. J. Bestmann, *Chem. Ber. 95* (1962) 58.
[2] a) H. J. Bestmann, *Angew. Chem. 77* (1965) 609, 651; *Angew. Chem. Int. Ed. Engl. 4* (1965) 583, 645; b) H. J. Bestmann, R. Zimmermann in Houben-Weyl: *Methoden der Organischen Chemie, 4 edit. Vol. E1*, Thieme, Stuttgart 1982, p. 636ff.
[3] H. Schmidbaur, *Acc. Chem. Res. 8* (1975) 62.
[4] R. Köster in Houben-Weyl: *Methoden der Organischen Chemie, 4th edit. Vol. XIII/3a*, Thieme, Stuttgart 1982, p. 378ff.
[5] For a different reaction of trialkylphosphonium ylides with halides of elements of the 1st–3rd main and sub-groups of the Periodic System cf. [3].
[6] A boron-substituted phosphonium ylide has been reported on but not isolated: D. S. Matteson, D. Majumda, *Organometallics 2* (1983) 230.
[7] For adducts of **1** and borane see H. J. Bestmann, K. Sühs, T. Röder, *Angew. Chem. 93* (1981) 1098; *Angew. Chem. Int. Ed. Engl. 20* (1981) 1038.
[8] B. A. Carlson, H. C. Brown, *J. Am. Chem. Soc. 95* (1973) 6876.

A Binuclear Molybdenum Complex with Two μ-Hydrazido(3−) *N*-Ligands

By *Rainer Mattes** and *Heinz Scholand*

Alkyl dithiocarbazates $NH_2NHC(S)SR$ are versatile ligands: thus, complexes with *N*-, *S*-, or *N,S*-coordinated neutral ligands are known, as are also chelate complexes of the singly (at N^α) or doubly (at N^α and N^β) deprotonated ligands[1]. Alkyl dithiocarbazates can also be used as starting substances for the synthesis of diazenido complexes[2]. In mononuclear compounds of this type the N_2R' group functions either as formal 3-electron donor with linear M−N−N arrangement or as 1-electron donor with angular M−N−N arrangement. For binuclear complexes with diazenido bridge-ligands, structure types **A**−**C** are conceivable; examples for all three cases are already known[3].



A **B** **C**

On attempting to convert the diazenido-hydrazido(1−)molybdenum complex **1**[2] into the corresponding hydrazido(2−) complex by protonation, we have now obtained the neutral, diamagnetic binuclear complex **2**[4].

The molybdenum complex **2** represents a novel example for the versatile ligand properties of alkyldithiocarbazates. As shown by an X-ray structure analysis[5] (cf. Fig. 1) the two molybdenum atoms in **2** are linked together via two N_2R' groups (R′ = C(S)SEt) analogously to the general type **A**; concomitantly, however, the two $N_2C(S)SEt$ groups function as N,S chelate ligands via the terminal sulfur atom. The bonding is best described in terms of the me-

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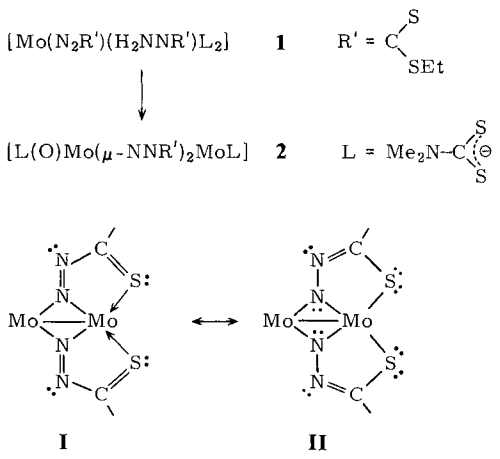

someric formulations **I** ↔ **II**. The coordination of the sulfur atoms lead to a preference for **II**. Therefore, in comparison to the previously known μ-diazenido *N*-complexes, the NN bond in **2** is elongated by more than 10 pm from 123 ± 1 pm to 135.0(8) pm. The novel complex **2** is thus to be designated as a hydrazido(3−)- and not as a diazenido-complex.

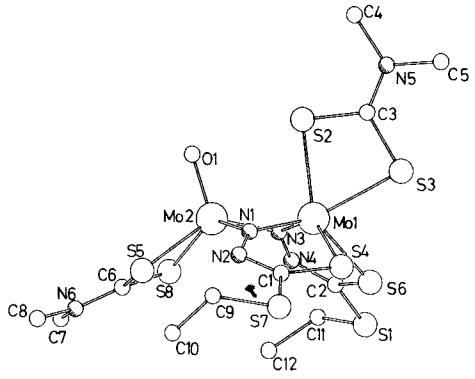

Fig. 1. Molecular structure of the binuclear molybdenum complex **2** in the crystal. Selected bond lengths [pm]: Mo1–Mo2 267.2(1), Mo1–N1 192.9(7), Mo1–N3 194.1(7), Mo1–S4 241.7(3), Mo1–S6 242.2(3), Mo2–N1 199.0(7), Mo2–N3 197.7(7), N1–N2 1.361(11), N2–C1 126.9(13), C1–S4 173.3(10), N3–N4 1.339(11), N4–C2 128.7(13), C2–S6 170.8(10); selected bond angles, mean values [°]: MoNMo 85.97(2), NNMo1 134.31(4), NNMo2 135.1(9), NMoN 91.0(3), dihedral angle NMo1N/NMo2N 152.5°. Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD 50792, the names of the authors, and the journal citation.

Further structure parameters support this hypothesis: The N^{β} atoms (N1 and N3) are not sp^2 hybridized. The sum of the bond angles to them is 353.9(5) and 357.0(5)°, respectively. The N^{α} atoms (N2 and N4) lie 30 and 40 pm, respectively, outside the Mo, N^{β}, Mo planes. The mean values of the N–C and C–S distances in the hydrazido ligands are 127.8(9) and 172.0(7) pm, and thus correspond to the values of CN double and CS single bonds, respectively. For hydrazido(3−) ligands the formal oxidation state of the central atoms of **2** is +5. Actually, the structural array with the Mo–Mo distance of 267.2(1) pm corresponds to that of numerous binuclear Mo^{V} complexes with metal-metal bonding and central $Mo_2O_2(\mu\text{-}O_2)$ groups[6]. However, as observed here for the first time, one of the two molybdenum atoms of **2** has no terminal oxygen or sulfur ligands; this coordination site is occupied rather by the two sulfur atoms of a $Me_2NCS_2^{\ominus}$ ion, without essentially changing the structure. The molybdenum atom concerned (Mo1) is surrounded by a trigonal-prismatic arrangement of four S atoms and two N atoms. To a good approximation **2** has C_s symmetry; the mirror plane is defined by the atoms O1, Mo1, and Mo2.

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CAS Registry numbers:
1, 84849-46-7; **2**, 89922-67-8; Mo, 7439-98-7.

[1] Cf. H. Weber, R. Mattes, *Chem. Ber. 113* (1980) 2833, and references cited therein.

[2] R. Mattes, H. Scholand, *Angew. Chem. 95* (1983) 246; *Angew. Chem. Int. Ed. Engl. 22* (1983) 245.

[3] C. F. Barrientos-Penna, F. W. B. Einstein, T. Jones, D. Sutton, *Inorg. Chem. 22* (1983) 2614, and references cited therein.

[4] a) Experimental procedure: A suspension of 0.6 g (approx. 1 mmol) [Mo[N_2C(S)SEt]{[NH_2NC(S)Et]{[Me_2NCS_2]$_2$] **1** in 40 mL methanol is treated with 1 mL conc. hydrochlorid acid and heated under reflux for 30 min. The color changes from reddish brown to deep red. The product **2** is filtered off and recrystallized from $CH_3OH/C_2H_4Cl_2$ (yield 53%), m.p. 97°C, correct elemental analysis; b) IR (KBr, cm^{-1}): 1572 sh, 1545 vs (νCN, L^1), 1400 vs (νCN, L^2), 1263 s, 1245 s ($\nu_{as}NC_2$, L^1), 1160 s (νCS, L^2), 1000 vs, 990 vs ($\nu_{as}CS_2$, L^1 and νNN, L^2), 945 vs (νMoO), 760 m, 730 m ($\nu_{as}Mo_2N_2$) [$L^1 = Me_2NCS_2$, L^2 = NNC(S)SEt].

[5] **2** crystallizes in the space group $P\bar{1}$, $a = 916.1(6)$, $b = 1033.0(7)$, $c = 1504.7(9)$ pm, $\alpha = 90.39(5)$, $\beta = 93.96(5)$, $\gamma = 115.20(5)°$, $Z = 2$; Syntex $P2_1$ diffractometer, 2946 independent reflections with $F_0 \geq 3.92\sigma(F_0)$, $2\vartheta_{max} = 48°$, 262 parameters, $R = 0.050$, $R_w = 0.056$, H atoms not located, all atoms refined anisotropically.

[6] E. I. Stiefel, *Prog. Inorg. Chem. 22* (1976) 1; R. A. D. Wentworth, *Coord. Chem. Rev. 18* (1976) 1.

Exhaustive Oxidative Decarbonylation of Metal Carbonyls by Light and Oxygen: The Example of $(\eta^5\text{-}C_5Me_5)ReO_3$**

By *Wolfgang A. Herrmann**, *Ricardo Serrano*, and *Hans Bock*

The photosensitivity of carbonylmetal compounds has been exploited for some considerable time to synthesize substituted derivatives[1]. To this end, one frequently selects the indirect route via photochemical generation of solvent-stabilized intermediates which are open for introduction of the desired ligands in subsequent dark reactions. A typical example of general preparative importance is the photochemistry of cymantrene, $(\eta^5\text{-}C_5H_5)Mn(CO)_3$, which via this method affords complexes of type $(\eta^5\text{-}C_5H_5)Mn(CO)_2L$ (L = two-electron ligand) that are frequently not accessible along other routes[1,2]. Whereas in the intermediate complex $(\eta^5\text{-}C_5H_5)Mn(CO)_2(THF)$ the cyclic ether ligand can readily be exchanged for better π-acceptors, in the analogous rhenium complex the considerably greater stability of the metal-oxygen bond renders further substitution reactions more difficult[3]. The much

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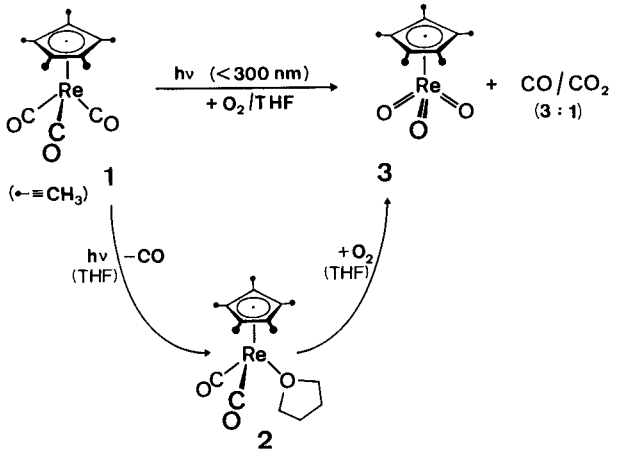
[**] Multiple Bonds between Main Group Elements and Transition Metals, Part 6. This work was supported by the Fonds der Chemischen Industrie, by the Deutsche Forschungsgemeinschaft, and by the Spanish Ministry of Education (post-doctoral fellowship to *R. S.*, 1982–84). We thank Prof. Dr. *D. Breitinger* (Universität Erlangen-Nürnberg) for the Raman spectrum. – Part 5: W. A. Herrmann, C. Hecht, M. L. Ziegler, B. Balbach, *J. Chem. Soc. Chem. Commun.*, in press.

higher oxophilicity of rhenium relative to that of manganese accounts for the remarkable formation tendency of the novel title compound **3**, too.



Irradiation of a solution of the half-sandwich complex **1** in tetrahydrofuran (THF) under rigorous exclusion of oxygen (argon atmosphere or vacuum, quartz glass, Hg high-pressure lamp) effects CO-elimination with formation of the THF complex **2**; the latter species has not yet been isolated in substance but its identity has been established from subsequent reactions with phosphanes. Whereas analogous manganese complexes decompose in the presence of atmospheric oxygen, **2** eliminates CO and CO_2 (GC) to form the carbonyl-free product **3**, which after work-up by means of column chromatography is obtained as air-stable, lemon yellow, sublimable crystals in up to ca. 40% yield[4]. **3** has the unexpected constitution of a mononuclear trioxo complex (MS, IR, Raman, NMR); elemental analysis and determination of M_r by vapor osmometry indicate the formula $C_{10}H_{15}O_3Re$ with only one Re atom[4]. **3** is derived from the educt **1** by oxidative substitution of the entire set of carbonyl groups by oxo ligands. The latter can be identified by their intense ν(Re=O) stretching bands (IR, Raman); the π-coordination of the pentamethylcyclopentadienyl ligands follows from the ^{1}H- and ^{13}C-NMR spectra, which even at -120°C ($CHFCl_2$) only exhibit simple signal patterns[4]. In terms of bonding theory, it is significant that the metal center in **1** is present in the oxidation state +1 (d^6-Re^I), but in **3**, for the first time in a half-sandwich complex, as Re^{VII} having a d^0 configuration. This enormous difference in the d-electron bookkeeping is reflected in the spectra. Thus, replacement of the CO by the oxo groups leads to a drastic deshielding ($\Delta\delta > 20$ ppm) of the C atoms of the ring ligands bonded to the metal in the ^{13}C-NMR spectrum, indicating a markedly reduced charge density. More impressive is that the PE spectra convincingly show the change in oxidation state: In the d^6 complex **1** (Fig. 1b) the first group of bands centered around 8 eV is assigned to the ionizations of metal d electrons, and the second at 9.2 eV to the almost degenerate π ionizations of the ring ligand[5]. As expected, for the trioxo complex **3** no further ionizations bands which could be assigned to metal d electrons are found in the low energy region of the PE spectrum (Fig. 1a)[6].

The results of a preliminary X-ray structure analysis indicate that the ring ligand is symmetrically π-bonded in the crystal[7]. Among the reactions of **3** investigated to date is its partial deoxygenation by triphenylphosphane. This is of

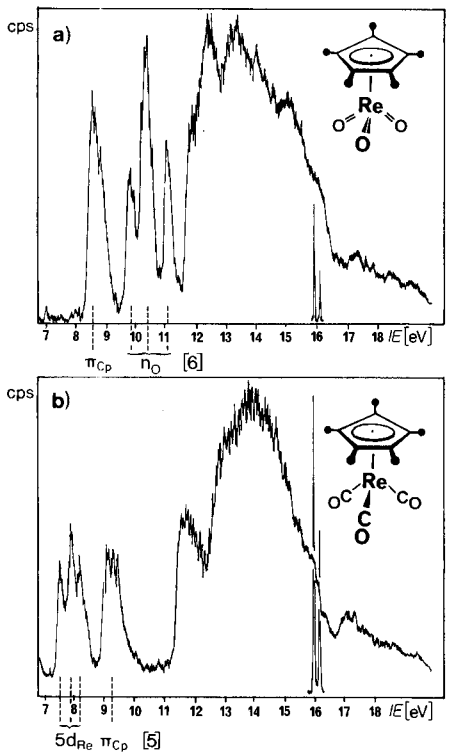
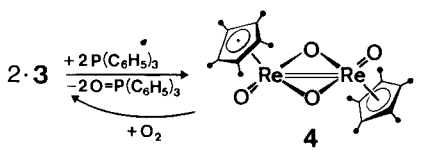


Fig. 1. He(I) PE spectra of a) trioxo- and of b) tricarbonyl(η^5-pentamethylcyclopentadienyl)rhenium recorded using a Leybold-Heraeus UPG 200 spectrometer at 10^{-5} mbar and 500 K (a) and 410 K (b). Calibrated with the $Ar(^2P_{3/2})$ peak at 15.76 eV; for assignment cf. [5, 6].

particular importance in that the binuclear derivative **4** is formed quantitatively and that this cleaves thermally into (η^5-C_5Me_5)ReO_2 fragments and hence makes secondary reactions accessible. Even in the solid state **4** rapidly rearranges in air to form the educt **3** (quantitative yield); this process corresponds to the formal change in oxidation state $Re^V \rightarrow Re^{VII}$[8]. Compound **4** reacts smoothly with bromine at -78°C in CH_2Cl_2 to give the mononuclear green complex (η^5-C_5Me_5)$ReOBr_2$ (air-sensitive), whereas reaction with CO (20 bar, toluene, 70 h) affords the title compound **3** as well as the carbonyl complex **1** and (η^5-



$C_5Me_5)_2Re_2(\mu\text{-}CO)_3$. Compound **3** also undergoes reductive carbonylation if it is allowed to react with (η^5-$C_5H_5)_2Ti(CO)_2$; in this case the rhenium-containing product is the crystalline, red oxo-complex (μ-O)[(η^5-C_5Me_5)$Re(CO)_2]_2$ (X-ray structure). The novel complex **3** is certainly comparable stoichiometrically with the tetrahedrally configurated derivatives CH_3ReO_3[9a] and $XReO_3$ (X = F, Cl, Br)[9b] but represents the first half-sandwich

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complex of the type $(\eta^5\text{-}C_5R_5)MO_x$ and, therefore, is the first representative of a novel class of compounds.

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[1] Review: G. L. Geoffroy, M. S. Wrighton: *Organometallic Photochemistry*, Academic Press, New York 1980.

[2] a) E. O. Fischer, M. Herberhold, *"Photochemische Substitutionsreaktionen an Cyclopentadienylmangan-tricarbonyl"*, in W. Schneider, G. Anderegg, R. Gut: *Essays in Coordination Chemistry, Exper. Suppl. IX*, Birkhäuser, Basel. 1964, p. 259–305; b) cf. P. M. Treichel in G. Wilkinson, F. G. A. Stone, E. W. Abel: *Comprehensive Organometallic Chemistry, Vol. 4*, ch. 29, Pergamon Press, Oxford 1982.

[3] D. Sellmann, E. Kleinschmidt, *Z. Naturforsch. B32* (1977) 795; cf. K. G. Caulton, *Coord. Chem. Rev. 38* (1981) 1, and N. M. Boag, H. D. Kaesz in [2b], ch. 30.

[4] *Procedure:* **1** (1.01 g, 2.5 mmol) is dissolved in 100 mL THF in a quartz glass Schlenk tube ($l = 25$ cm, $\varnothing = 3.4$ cm). The reaction vessel is sealed and evacuated until the solution foams up. Subsequently, the vessel is placed at ca. 4 cm distance from a water-cooled lamp housing (quartz glass) in which an Hg high-pressure lamp (TQ 150, Original Hanau) is located. The solution is stirred and irradiated for 8 h (solution temperature 30–40°C). At 2 h intervals the mixture is filtered *in air* and the clear, yellow-brown filtrate is stored in an open flask for 15 h, subsequently concentrated in vacuo, and the residue chromatographed on a silica gel column (Merck 7734, Act. II–III; $l = 40$ cm, $\varnothing = 1.2$ cm). Small amounts of unreacted **1** as well as unidentified side products are eluted with benzene. **3** is then eluted in a bright yellow zone using toluene/diethyl ether (1 : 2 v/v). The crude product is washed with 20 mL *n*-hexane and recrystallized from diethyl ether/dichloromethane (2 : 1 v/v; +25 ... −35°C); by this means, **3** forms as refractive, lemon-yellow needles, which are both stable in air and up to temperatures above 140°C (slow decomposition with brown coloration upon prolonged heating in the temperature range 150–200°C; no definite melting point). Yield 296–379 mg (32–41%); insoluble in aliphatic hydrocarbons, very soluble in CH_2Cl_2, toluene, and THF. ^{1}H-NMR (270 MHz, C_6D_6, 26°C): δCH_3 1.63 (s); ^{1}H-NMR (270 MHz, CD_2Cl_2, −80°C): δCH_3 2.08 (s); no signal broadening at this temperature.—$^{13}C\{^1H\}$-NMR ($CDCl_3$, 28°C): δCH_3 10.24, δC_5Me_5 120.35.—IR (KBr): 909 s-vs, 878 vs, [ν_{as}(Re=O)]; further bands 334 w, 393 m, 797 w-m, 960 w, 1024 m, 1073 w, 1362 m, 1373 m, 1381 m, 1440 m (br), 1472 w (br), 1504 m; 2920–3000 w-m [ν(CH)].—IR [CS_2; ν_{as}(Re=O)]: 922 s-vs, 892 vs.—Raman [solid; ν(Re=O)]: 907 vs, 889 m, 874 w-m (C_s-symmetry).—MS (Varian MAT CH7; 12 eV $T_Q = 100$°C, $T_E = 120$°C, ^{187}Re): $M^{\oplus\odot}$ (*m/z* 370, rel. int. 100%), $[M-O]^{\oplus\odot}$ (354, 32), $[M-2O]^{\oplus\odot}$ (338, 40), $C_{10}H_{15}^{\oplus\odot}$ (135, 96; with decomposition spectrum, $m/z < 135$).—FD-MS: 370 (parent ion, ^{187}Re).—Correct elemental analysis (C, H, Re, O).

[5] D. C. Calabro, J. L. Hubbard, C. H. Blevins II, A. C. Campbell, D. L. Lichtenberger, *J. Am. Chem. Soc. 103* (1981) 6839, and literature cited therein. The PE spectrum of **1** was assigned by comparison of the radical cation state with those of the similar complexes $CpRe(CO)_3$, $CpMn(CO)_3$, and $Me_5CpMn(CO)_3$ on the basis of the observed vibrational fine structure and with parameter-free Fenske/Hall model calculations: Accordingly, the group of bands around 8 eV contains the metal d-states $\tilde{X}(^2E_{3/2})$ and $\tilde{B}(^2E_{1/2})$ split by spin/orbit coupling to $\tilde{A}(^2A_1)$ under the local C_{3v} symmetry, and the second group of bands at ca. 9.2 eV the states $\tilde{C}(^2E'')$, which are almost degenerated under the local D_{5h} symmetry, with predominant π Cp contribution.

[6] Because of the unexpectedly large relaxation and correlation effects, the PE spectra of organometallic compounds cannot usually be assigned on the basis of MO calculations and Koopman's theorem (cf. e.g. M. C. Böhm, *Inorg. Chem. 22* (1983) 83, and literature cited therein). For the novel title compound, comparison of the radical cation state with similar complexes is also not possible. Qualitative considerations—starting from the intensity ratio 2 : 1 : 2 : 1 of the four PE bands of lowest energy and the C_5H_5 π-system as well as the oxygen lone-pairs n_O, which are the most electron-rich sites in the Re(d^0) compound **3**, and which can each be subdivided into three parallel (∥) and three horizontal (⊥) components—lead to the proposed assignment $\pi_{Cp}(e) < n_O^{\perp}(a_2) < n_O^{\parallel}(e) < n_O^{\perp}(a_1)$. The missing degenerate combination $n_O^{\parallel}(e)$ should be stabilized by overlap with d_{xz}(Re) and d_{yz}(Re). An EHMO-approximation calculation for the (still) fictitious $CpMnO_3$ with program-specific standard parameters reproduces this qualitative MO sequence.—Cf. J. C. Green, S. E. Jackson, B. Higginson, *J. Chem. Soc. Dalton Trans. 1975*, 403.

[7] H. Nöth, Universität München, personal communication.

[8] Spectroscopic data for **4** (brown crystals): IR (νReO, cm^{-1}, KBr): 930 s (terminal); 634 s, 614 m (bridging). ^{1}H-NMR (CD_2Cl_2, 28°C): $\delta CH_3 = 2.03$ (s). Correct elemental analysis (C, H, Re, O). W. A. Herrmann, R. Serrano, A. Schäfer, M. L. Ziegler, E. Guggolz, *J. Organometal. Chem.*, in press.

[9] a) I. R. Beattie, P. J. Jones, *Inorg. Chem. 18* (1976) 2318, and literature cited therein; b) cf. K. Dehnicke, W. Liese, *Chem. Ber. 110* (1977) 3959.

Dextran-Linked N^6-(2-Isopentenyl)adenosine—A Polymer-Bound Antimetabolite with a Predetermined Cleavage Position**

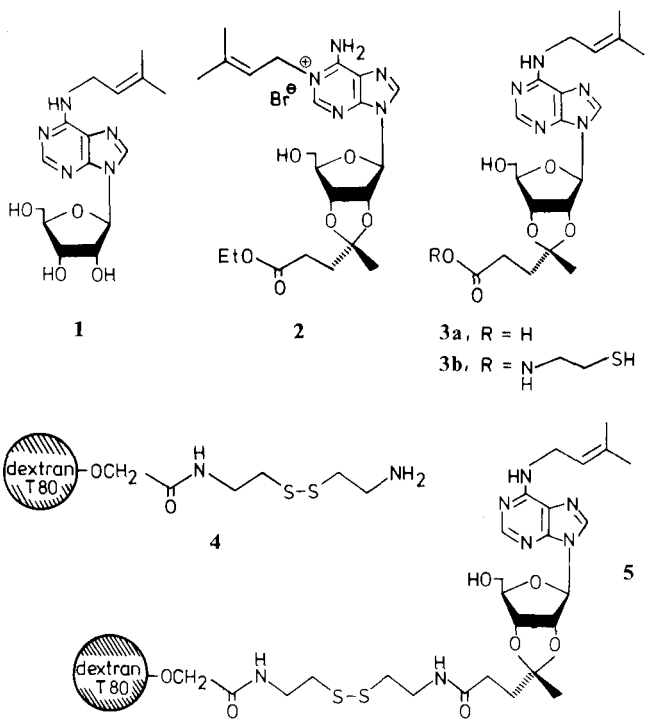
By *Helmut Rosemeyer* and *Frank Seela**

N^6-(2-Isopentenyl)adenosine [6-(3-methyl-2-butenylamino)-9-ribosylpurine, i^6A], **1**, is a modified nucleoside which exhibits cytokinine activity and stimulates cell division and cell differentiation. It is found in the *t*RNA's of many organisms and, furthermore, shows strong antitumor activity in transformed cells, animals, and man[1].

The covalent attachment of **1** to biopolymers (e.g. dextrans) is expected to increase the circulatory lifetime (plasma half-life) of **1** and would alter the uncontrolled distribution of the pharmacon over the compartments of the organism. Furthermore, polymer-linked anticancer drugs should show an enhanced tumor cell selectivity since the latter possess an increased pinocytic uptake activity compared to normal cells[2].

Dextrans which contain linear chains of 1→6—linked α-D-glucopyranose residues as the dominant structural feature have proven valuable as biopolymeric carriers for biologically active compounds since they can be slowly hydrolyzed by dextranases in vivo. Dextran is used as a blood-volume expander in the molecular-weight range 4×10^4–8×10^4[3].

We report here on the covalent attachment of **1** via a cyclic acetal side chain to activated dextran T 80 bearing a spacer with a disulfide bridge as a predetermined cleavage position. Furthermore, we describe the chemically controlled release of the derivative **3b** of **1** from the polymer **5** by reduction of the disulfide bridge of the spacer using dithiothreitol. This can serve as a model reaction for a drug delivery by reducing enzymes like glutathione reductase.



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Alkylation of (*R*)-2′,3′-*O*-(3-ethoxycarbonyl-1-methylpropylidene)adenosine[4] with 1-bromo-3-methyl-2-butene in dimethylformamide (DMF) leads to **2**. Dimroth rearrangement with simultaneous saponification of the ester function in the acetal side chain yields the acid **3a**[5]. Its structure could be confirmed by ^{1}H- and ^{13}C-NMR spectroscopy. The ribose ring conformation of **3a** was determined from the observed vicinal proton coupling constants [$J_{2',3'}$ and $(J_{1',2'}+J_{3',4'})$], which allow an estimation of the corresponding pseudorotational parameter (P, τ_m) using the nomograms in ref. [6]. The parameters were found to be: $P_N=231°$; $P_S=219°$; $\tau_m=42°$. From these data the S-conformer population ([S], C-3′-*exo*) was calculated to 50%, which corresponds to a $^4_3$T conformation. The data of the unmodified nucleoside, however, imply a ^{2}E-conformation which demonstrates the altered sugar puckering caused by the chemical modification[7].

The modified dextran **4** bearing a spacer with a predetermined "breaking point" was prepared by carboxymethylation of dextran using chloroacetate in a strong alkaline medium to form carboxymethylated dextran T 80 (CM-dextran). Reaction of CM-dextran with cystamine in water using *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (EDC) as coupling reagent yielded the polymer **4**, which could be isolated as a water-soluble and fluffy solid after dialysis and lyophilization[8].

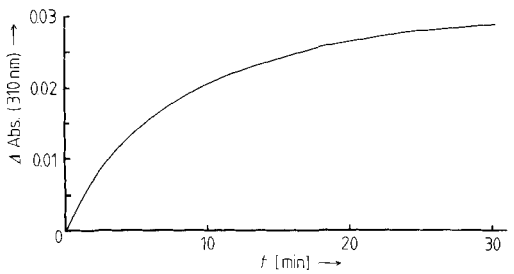

Fig. 1. Dithiothreitol cleavage of **5** as a function of time in Sørensen phosphate buffer (0.07 M, pH 7.6, 10^{-3} M EDTA) with dithiothreitol (10 μL of an 0.5 M aqueous solution, 10^{-3} M EDTA). The formation of 1,2-dithiane-4,5-diol was monitored at $\lambda=310$ nm.

The activated dextran **4** was coupled with the acid **3a** to give **5**[10]. As can be seen from Figure 1, the half-life of the reduction is about 15 min and the reaction does not show simple first-order kinetics. This implies that an in vivo release of the ligand **3b** by reducing enzymes like glutathione reductase can be accomplished—a process which may be of general importance for the delivery of pharmacologically active compounds.

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[3] L. Molteni in G. Gregoriadis: *Drug Carriers in Biology and Medicine*. Academic Press, New York 1979, p. 107.
[4] F. Seela, F. Cramer, *Chem. Ber. 108* (1975) 1329.
[5] **3a**: (*R*)-2′,3′-*O*-(3-Ethoxycarbonyl-1-methylpropylidene)adenosine [4] (1 g, 2.54 mmol) was dissolved in dry dimethylformamide (10 mL) and 1-bromo-3-methyl-2-butene (5 g, 33.6 mmol) was added. The reaction mixture was stirred for 24 h in the dark at room temperature. After evaporation to dryness in high vacuo the residue was dissolved in water (50 mL) and the pH was adjusted to 12 by adding 1 N NaOH. The solution was heated at 50°C on a water bath for 3 h while the pH was held constant. After acidification to pH 5 with 1 N HAc the reaction mixture was extracted four times with ethyl acetate 100 mL, each). The combined extracts were dried over sodium sulfate and evaporated to dryness. The residue was dissolved in water (5 mL), and **3a** was crystallized by addition of a few drops of glacial acetic acid. Recrystallization from acetonitrile/ethanol (1:1) gave 320 mg (20%) of **3a**, m.p. 170°C. TLC (silica gel, $CHCl_3$–MeOH, 7:3), $R_f=0.55$; UV (MeOH): $\lambda_{max}=268$ nm ($\varepsilon=18\,500$ M^{-1} cm^{-1}).—^{13}C-NMR ([D$_6$]Me$_2$SO): $\delta=174.07$ (C=O), 154.38 (C-6), 152.57 (C-2), 146.50 (C-4), 139.49 (C-8), 133.21 (C=), 122.07 (C-5), 118.60 (CH=), 113.91 (C-acetal), 89.56 (C-1′), 86.58 (C-4′), 83.34 (C-2′), 81.34 (C-3′), 61.46 (C-5′), 38.14 (N^{6}CH$_2$), 33.74 (CH$_2$C=O), 28.30 (CH$_2$-acetal), 25.26 (CH_3 (E), dimethylallyl moiety), 23.51 (CH_3-acetal), 17.74 (CH_3 (Z), dimethylallyl moiety).—^{1}H-NMR ([D$_6$]Me$_2$SO): $\delta=8.32$ (1H, s, 2-H), 8.23 (1H, s, 8-H), ~7.9 (s, NH), 6.15 (1H, d, 1′-H, $J=2.4$ Hz), 5.42 (1H, dd, 2′-H, $J_{2'\text{-H}/1'\text{-H}}=2.5$ Hz, $J_{2'\text{-H}/3'\text{-H}}=6.3$ Hz), 5.30 (1H, t, CH=, $J=6.4$ Hz), 5.02 (1H, dd, 3′-H, $J_{3'\text{-H}/4'\text{-H}}=2.3$ Hz, $J_{3'\text{-H}/2'\text{-H}}=6.4$ Hz), 4.22 (1H, m, 4′-H), 4.19 (s, broad, OH), 3.48 (m, 5′-H), 2.41 (2H, t, CH$_2$, $J=8.1$ Hz), 2.04 (2H, t, CH$_2$, $J=8.1$ Hz), 1.70 (3H, s, CH_3), 1.67 (3H, s, CH_3), 1.31 (3H, s, CH_3-acetal).
[6] Evaluation with the nomograms in W. Guschlbauer, T.-D. Son, *Nucleic Acids Res. Spec. Publ. 1* (1975) 131.
[7] E. Westhof, O. Röder, J. Croneiss, H.-D. Lüdemann, *Z. Naturforsch. C30* (1975) 131.
[8] **4**: Carboxymethylated dextran T 80 [9] (1.3 g) was dissolved in water (35 mL), and cystamine hydrochloride (5 g, 22.2 mmol) was added. After adjustment of the pH to 4–5, EDC·HCl (350 mg, 1.83 mmol) was added in small portions during the next 3.5 h. The solution was dialyzed for 5 days against water (5 changes daily) and lyophilized to yield 1.2 g of **4**. The polymer shows a positive ninhydrin reaction and was free of cystamine impurities which could be demonstrated by TLC (silica gel, 0.25 M LiCl). The ligand concentration of **4** (3.15 mg) was determined spectrophotometrically at 260 nm using the extinction coefficient of cystamine at that wavelength ($\varepsilon=380$ M^{-1} cm^{-1}), and was found to be 410 μmol/g (33 mol/mol) **4**.
[9] J. K. Inman, *J. Immunol. 114* (1975) 704.
[10] **5**: The acid **3a** (50 mg, 0.12 mmol) was dissolved in water/dioxane (20 mL, 1:1) and **4** (0.35 g) was added. After shaking for 5 min at room temperature EDC·HCl (250 mg, 1.3 mmol) was added. After shaking for another 12 h at room temperature the solution was chromatographed on Sephadex G-50 (2.5 × 60 cm). Lyophilization yielded **5** (0.35 g). The ligand concentration was determined spectrophotometrically at 268 nm using the extinction coefficient of **3a**, and was found to be 12.9 μmol of **3a**/g of dextran.

Bis(1,3,5-trimethylbenzene)indium(I) Tetrabromoindate(III), the First Arene Complex of Indium

By *Jan Ebenhöch, Gerhard Müller, Jürgen Riede,* and *Hubert Schmidbaur**

Dedicated to Professor Jan Thesing and the occasion of his 60th birthday

Arene complexes of transition metals[1] have played an important role in organometallic chemistry ever since the discovery of bis(benzene)chromium[2], yet rarely has any attention been paid to the fact that some main group elements in low valency states also readily form coordination compounds with aromatic hydrocarbons. It was first demonstrated by *Amma* et al.[3] that, e.g., Sn^{II} atoms, like transition metal atoms, can coordinate centrally to a benzene ring. However, until quite recently, elucidation of the structure of such compounds has been restricted to mono(arene) complexes.

In continuation of a systematic study on this new class of compounds we have been able to prepare, besides the (η^6-hexamethylbenzene)gallium(I) ion, both the bis(benzene)gallium(I) complex as well as the bis(mesitylene)gallium(I) complex and to examine them X-ray crystallogra-

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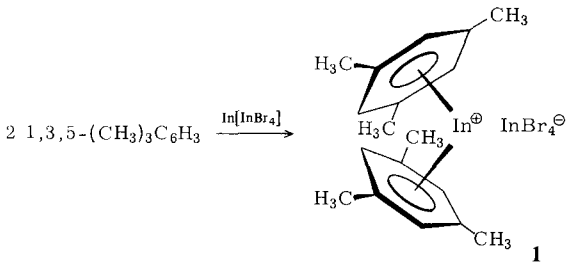
[+] X-ray structure analysis.

phically[4]. Herein we report on the title compound **1**, the first compound containing a bis(arene)-complex of indium.

Anhydrous mesitylene (1,3,5-trimethylbenzene) saturated with nitrogen rapidly takes up considerable amounts of $In(InBr_4)$ on heating; the $In[InBr_4]$ may be generated separately or in situ[5]. On cooling such solutions, colorless crystals are formed whose elemental analysis reveals a ratio of reactants of 2 : 1. The product is sensitive to air and light and—particularly on reducing the pressure—soon loses a part of its arene content.



1

The X-ray structure analysis of **1**[6] shows that the compound in the crystalline state is a coordination polymer whose helical chains run along the y axis; complex cations and anions are coupled in such a way that the tetrabromoindate(III) tetrahedra are bidentate chelate-forming on one side and monodentate-bridging on the other (cf. Fig. 1).

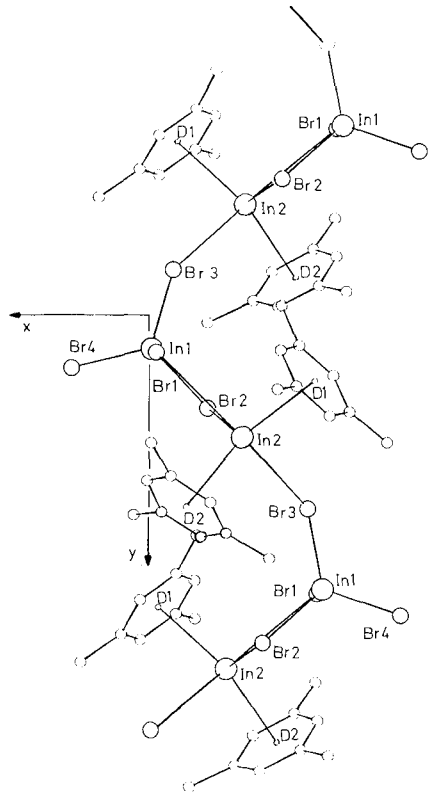


Fig. 1. Projection of a section of the crystal structure of **1** on the x,y plane.

The environment of each In^{I} center (In2) is completed by two mesitylene rings, which are inclined to each other at an angle of 47.3°. Their centroids are at about the same distance from the metal atom, which is located almost perpendicularly over the center of the ring (Fig. 2). The three bromine atoms are arranged in a plane bisecting the angle between the hydrocarbon rings in such a way that the BrInBr angles are almost equal, even though two of the halogen atoms (Br1, Br2) are coordinated as part of a chelate ligand (Fig. 2 and 3).

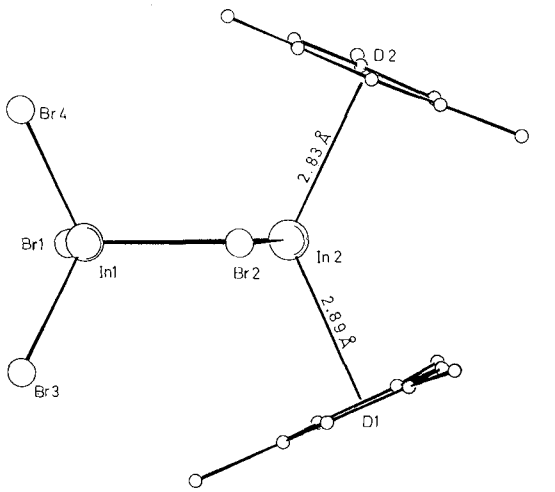


Fig. 2. Sideview of a monomeric unit of **1**.

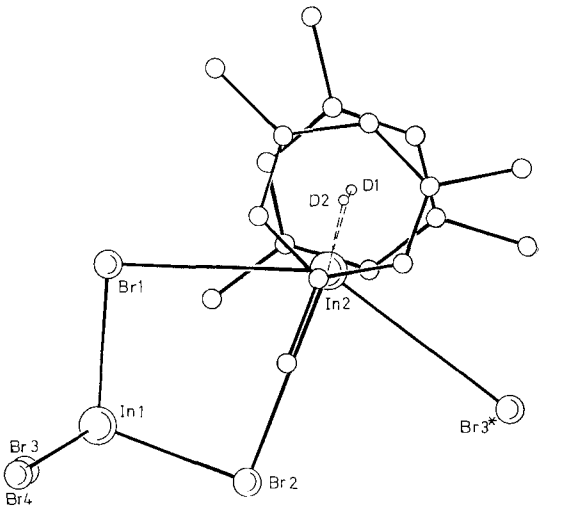


Fig. 3. Projection of the molecule **1** on the plane through In2, Br1, Br2, Br3 (cf. Fig. 1). Selected bond lengths [Å] and angles [°]: In1–Br1 2.494(1), In1–Br2 2.500(1), In1–Br3 2.482(1), In1–Br4 2.466(2), In2–Br1 3.446(1), In2–Br2 3.503(1), In2–Br3* 3.527(1); Br1–In1–Br2 106.3(1), In1–Br1–In2 92.4(1), In1–Br2–In2 91.0(1), In2–Br3*–In1* 146.0(1), Br1–In2–Br2 70.2(1), Br2–In2–Br3* 74.1(1).

The structure of **1** reveals many analogies to transition metal arene complexes[1]. However, because of the electronic configuration $5s^25p^04d^{10}$ of the main group element indium, a completely different situation arises for a theoretical description. Simple model concepts such as the noble gas rule must therefore be replaced in this instance and in related problems by the cluster formalism[7] or a specific MO consideration[8]. We have also obtained crystals of the arene complexes $[1,3,5\text{-}(CH_3)_3C_6H_3]_2In^{\oplus}AlBr_4^{\ominus}$ and $[(CH_3)_6C_6]In^{\oplus}InBr_4^{\ominus}$, whose characterization is still under

way. Unsubstituted benzene is so loosely bound to In[1] that the adducts could so far not be isolated.

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[5] B. H. Freeland, D. G. Tuck, *Inorg. Chem. 15* (1976) 475; P. L. Radloff, G. M. Papatheodorou, *J. Chem. Phys. 72* (1980) 992.
[6] $C_{18}H_{24}Br_4In_2$, $M_r = 789.648$; monoclinic, $P2_1/n$, $a = 10.624(2)$, $b = 13.384(3)$, $c = 17.697(4)$ Å, $\beta = 94.56(2)°$ at $-40°C$, $V = 2508.4$ Å^3, $Z = 4$, $\rho_{calc} = 2.091$ g cm^{-3}, F(000) = 1480; 3946 independent reflections, 783 unobserved ($I < 2.0\sigma(I)$); Syntex $P2_1$, $Mo_{K\alpha}$, $\lambda = 0.71069$ Å, ω scan, $1° \leq \vartheta \leq 24°$); empirical absorption correction ($\mu = 81.24$ cm^{-1}), based on ψ scans of 10 reflections; solution by direct methods (MULTAN); $R = 0.047$, $R_w = 0.051$, atoms other than H anisotropic, H atoms (calculated) constant (SHELX 76), $\Delta\rho_{max} = 1.15$ e/Å^3. Further details of the crystal structure analysis are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD 50759, the names of the authors, and the journal citation.
[7] K. Wade, *Adv. Inorg. Chem. Radiochem. 18* (1976) 1; R. E. Williams, *ibid. 18* (1976) 67.
[8] P. F. Rodesiler, T. Auel, E. L. Amma, *J. Am. Chem. Soc. 97* (1975) 7405.

Bonding Attitudes in Crystalline SeF_4 and TeF_4**

By *Rüdiger Kniep*, Lutz Korte, Rainer Kryschi,* and *Wolfgang Poll*

Selenium tetrafluoride: In solution, the SeF_4 molecule has a pseudo-trigonal-bipyramidal structure; with increasing concentration, the molecules become increasingly associated via intermolecular fluorine bridges[1]. We have now succeeded in determining the crystal structure of SeF_4 and are able to comment on the type of intermolecular interactions and the molecular structure. From the very beginning, it could not be ruled out that crystalline SeF_4 is also polymeric, like TeF_4. Since the structure analysis of TeF_4 reported in the literature[2] (film technique) gave only relatively inaccurate bond lengths and angles, we have also redetermined the structure of TeF_4, a comparison of the bonding in SeF_4 and TeF_4 thus becoming more informative.

SeF_4 and TeF_4 were prepared by reactions of SeO_2 and TeO_2, respectively, with SF_4 in an autoclave[3,4], and were subsequently purified by distillation or vacuum sublimation. In the case of TeF_4 (m.p. 130°C), single crystals for the structure analysis were already obtained on sublimation, while in the case of SeF_4 (m.p. $-10°C$) they were cultivated from the melt on the single-crystal diffractometer. Determination of the lattice parameters and measurement of the reflection intensities were carried out on both compounds at $-110°C$. SeF_4 and TeF_4 crystallize with similar lattice metrics in the space group $P2_12_12_1$; remarkable, however, is that the *c*-axis in TeF_4 is considerably shorter than that in SeF_4[5].

The molecular structure and coordination of the compounds are shown in the top part of Figure 1. In SeF_4 the

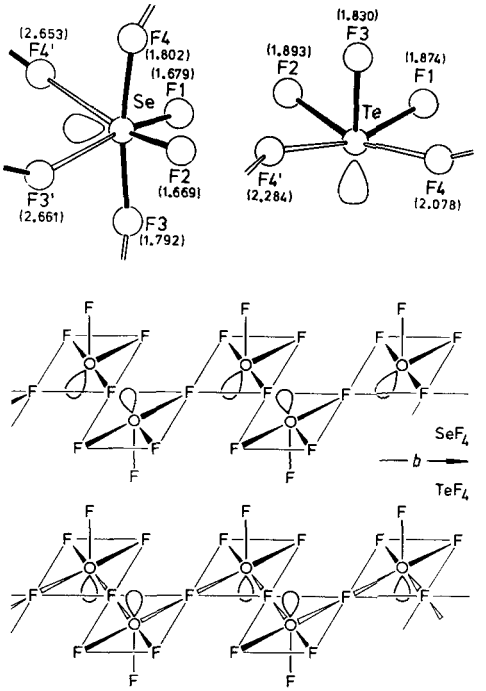

Fig. 1. *Top:* Molecular structure and coordination in SeF_4 and TeF_4 with bond lengths (standard deviations 0.006 and 0.005 Å, respectively). Bond angles (standard deviations 0.3 and 0.2°, respectively): F1SeF2 96.9, F1SeF3 85.7, Fe1SeF4 87.2, F1SeF3' 171.0, F1SeF4' 77.1, F2SeF3 85.5, F2SeF4 87.5, F2SeF3' 78.5, F2SeF4' 169.5, F3SeF4 169.3, F3SeF3' 86.3, F3SeF4' 102.5, F4SeF3' 100.3, F4SeF4' 83.6, F3'SeF4' 108.6, SeF3Se' 150.1, SeF4Se'' 139.9.—F1TeF2 86.8, F1TeFe3 87.6, F1TeF4 83.9, F1TeF4' 162.5, F2TeF3 84.2, F2TeF4 161.3, F2TeF4' 88.2, F3TeF4 79.2, F3TeF4' 75.3, F4TeF4' 95.9, TeF4Te' 154.1.—*Bottom:* Polymeric structure in TeF_4 and position and sequence of monomers in a corresponding section of the SeF_4 structure (schematic representation).

selenium is bonded to four fluorine atoms in such a way that, with the pair of electrons on the selenium atom also taken into consideration, a distorted pseudo-trigonal bipyramid with longer axial Se–F bonds results. In accord with the electron pair repulsion (VSEPR) model the F_{ax}–Se–F_{ax} array is not linear but angular (169.3°), with the Se–F_{ax} bonds tilting away from the lone pair on Se; in the same way, the F_{eq}–Se–F_{eq} angle is smaller than 120°. The coordination of neighboring molecules in the second sphere is increased via the axial fluorine atoms (distorted octahedral fluorine coordination); according to the size of the F···Se distance, the intermolecular interactions are to be rated as being so weak that they do not significantly influence the bonding in the SeF_4 molecule. The bonding in TeF_4 is different (see also [2]). Here the tellurium is bonded to five fluorine atoms (distorted tetragonal pyramid), two of which (*cis*-oriented in the tetragonal plane) bridge a further neighboring tellurium atom each. The bridge bonds, are, however, distinctly shorter than the intermolecular F···Se contacts in SeF_4. It is to be expected that the lone pair on the tellurium completes a pseudo-octahedral coordination of the central atom; consistent with this expectation the tellurium atom is located 0.3 Å below the plane of the four fluorine atoms. The differences in the bonding in crystalline SeF_4 and TeF_4 can be ascribed to the respective degrees of hybridization of the chalcogen, and can be described in terms of sp^3d (SeF_4: pseudo-trigonal-bipyramidal) and sp^3d^2 states (TeF_4: pseudooctahedral). The polymeric structure of TeF_4 in the [010] direction and the position and sequence of SeF_4 monomers (also in the [010] di-

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rection) in a corresponding section of the SeF_4 structure are reproduced schematically at the bottom of Figure 1. The shortening of the *c*-axis in TeF_4 is due to the strong fluorine bridges within the polymeric structural assemblage. The fundamental similarity of the arrangements of the structural units of SeF_4 and TeF_4 in the [010] direction also exists in the three-dimensional crystal arrays. The possibility of a structural transformation in SeF_4 by a closer (pressure-induced) proximity of the axial fluorine atoms to selenium atoms of neighboring molecules cannot be ruled out.

The chemical similarity of SeF_4 and SF_4[6] seems to be further confirmed by the—albeit up to -160 °C disordered—crystal structure of SF_4[7], from which a formation of fluorine-bridged associates in crystalline SF_4 is not to be assumed.

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[4] D. Lentz, H. Pritzkow, K. Seppelt, *Inorg. Chem. 17* (1978) 1926.
[5] Crystallographic data: SeF_4: 1220 (1378) reflections; $R = 5.9\%$; $P2_12_12_1$; $a = 5.169(1)$, $b = 5.548(1)$, $c = 11.345(2)$ Å; $Z = 4$; $\rho_{calc} = 3.16$ g/cm³.—TeF_4: 1525 (1608) reflections, $R = 6.0\%$; $P2_12_12_1$; $a = 5.214(4)$, $b = 6.229(5)$, $c = 9.414(7)$ Å; $Z = 4$; $\rho_{calc} = 4.37$ g/cm³. Further details of the crystal structure investigation are available from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD 50827, the names of the authors, and the journal citation.
[6] K. Seppelt, *Angew. Chem. 91* (1979) 199; *Angew. Chem. Int. Ed. Engl. 18* (1979) 186.
[7] L. Korte, Dissertation, Universität Düsseldorf 1983.

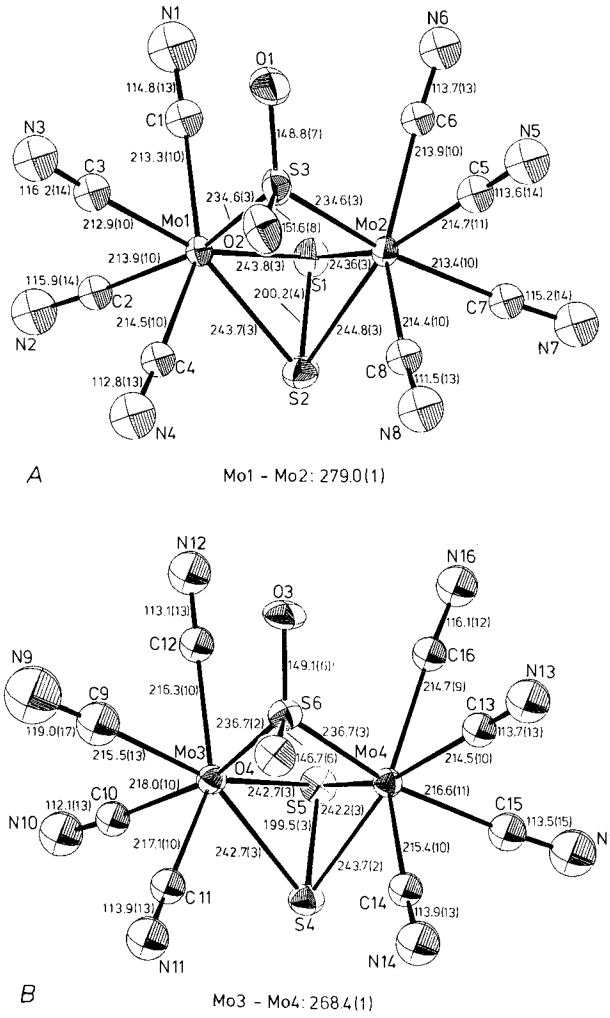

Fig. 1. ORTEP plot of the complex anions at the positions *A* and *B* in the asymmetric unit of crystals of **1** [4] (distances in pm). Further details of the crystal structure determination are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD 50676, the names of the authors, and the journal citation.

Mixed Crystals Containing the Diamagnetic Complex $[Mo_2(SO_2)(S_2)(CN)_8]^{4\ominus}$ and the Paramagnetic Complex $[Mo_2(SO_2)(S_2)(CN)_8]^{5\ominus}$

By *Achim Müller**, *Werner Eltzner*, *Rainer Jostes*, *Hartmut Bögge*, *Ekkehard Diemann*, *Jürgen Schimanski*, and *Heiko Lueken*

Paramagnetic multinuclear and, particularly, binuclear complexes of the heavy transition metals (4d and 3d elements) are rare. We have now been able to isolate a compound which contains the isostructural anions $[(Mo^{III/IV})_2(SO_2)(S_2)(CN)_8]^{5\ominus}$ **1a** (paramagnetic) and $[(Mo^{IV})_2(SO_2)(S_2)(CN)_8]^{4\ominus}$ **1b** (diamagnetic)[1] *together* in a mixed crystal compound.

Passage of oxygen into an aqueous solution of $[(Mo^{III})_2(S)_2(CN)_8]^{6\ominus}$ **2**[2] leads to the formation of a blackish violet mixed-crystal compound of the composition $K_{4+x}[(Mo^{III/IV})_2(SO_2)(S_2)(CN)_8]_x[(Mo^{IV})_2(SO_2)(S_2)(CN)_8]_{1-x} \cdot 4H_2O$ **1** ($x = 0.3$) **1**[3]. **1** was characterized magnetochemically and spectroscopically (ESCA, ESR, IR, UV/VIS/NIR), and by an X-ray structure analysis (Fig. 1)[4].

In the crystal, the complexes **1a** and **1b** are located at two crystallographically independent positions *A* and *B* (Fig. 1). The structures of **1a** and **1b** differ only slightly; in both complexes each molybdenum atom is surrounded by an approximately pentagonal-bipyramidal array of four $CN^{\ominus}$ and three sulfur atoms of the bridging ligands $SO_2^{2\ominus}$[1] and $S_2^{2\ominus}$[5]. However, markedly different Mo–Mo bond lengths are observed for the positions *A* and *B* (279.0 and 268.4 pm, respectively). Since the greater Mo–Mo distance is to be expected for **1a** (see below), this complex obviously preferably occupies the position *A*; but since the crystal contains only ca. 30% of **1a**, the geometric parameters cannot exclusively arise from **1a**, at least in the case of *A*.

By ESCA measurements[6] it was possible to demonstrate that mixed valence Mo species are present in **1**. Moreover, from the hyperfine structure of the ESR spectrum (solution of **1** in water, addition of Na_2SO_3[7], room temperature) it unequivocally follows that an unpaired electron in **1a** interacts with the nuclear spin of two chemically equivalent Mo atoms (^{95}Mo and ^{97}Mo with $I = 5/2$). The measured parameters $\bar{g} = 2.012$ and $\bar{A}(^{95}Mo) = 19.2$ G

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point to a strong delocalization of the unpaired electron (e.g. in comparison to that in $[Mo_2(SO_4)_4]^{3\ominus}$[8]).

The electronic absorption spectrum of **1** in aqueous solution (addition of Na_2SO_3[7]) reveals the presence of both **1a** (980, 340 (sh), 305 nm) and **1b** (900, 550, 410 (sh), 340, 280 (sh), 230 nm)[9]. The time-dependent measurement of the IR spectra of an aqueous solution of **1**, through which O_2 is passed, permits monitoring of the conversion of **1a** (ν(CN): 2103 cm^{-1}) into **1b** (ν(CN): 2134 cm^{-1}); the ESR signal of **1a** correspondingly disappears.

The proportion of the binuclear unit **1a** in the mixed crystal was estimated from susceptibility measurements (Faraday method) to be 31%[10].

An SCCC-EH-MO calculation on **1b** showed that the species can be best described as a $(Mo^{IV})_2/SO_2^{2\ominus}/S_2^{2\ominus}$ complex with a metal-metal double bond (two occupied MOs with pronounced Mo-4d character, configuration approximately $\sigma^2\pi^2$); formally, the 18-electron rule is fulfilled. The additional electron in **1a** occupies a weakly Mo–Mo antibonding MO ($\sim\delta^*$), from which the greater atomic distance is feasible.

Also remarkable is the reaction path leading to **1**. Passage of O_2 into a solution of **2** leads to successive formation of $[(Mo^{IV})_2(S)_2(CN)_8]^{4\ominus}$ **3**[11], **1a**, and **1b**:

$$\mathbf{2} \xrightarrow[(a)]{O_2} \mathbf{3} \xrightarrow[(b)]{(O_2)} \mathbf{1a} \xrightarrow[(c)]{O_2} \mathbf{1b}$$

Under the given conditions[3], **1a** and **1b** crystallize out together in the mixed-crystal compound **1**. In the case of reactions (a) and (c) the conversion of isostructural species with different electron populations takes place via two- and one-electron oxidation processes, respectively (detection by CV measurements on **2** and **3**[11] and **1b**: $E_{1/2} = 0.06$ V relative to the potential of the normal hydrogen electrode), whereas reaction (b) involving formation of the $SO_2^{2\ominus}$ and $S_2^{2\ominus}$ bridging-ligands is more complicated and not understood.

According to *Robin* and *Day*[12], the salt **1** can be classified as a mixed-valence compound of type I, while the anion **1a** can be assigned to the type III (complete delocalization).

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CAS Registry number:
2·6K, 71788-85-7.

[1] The oxidation states of the molybdenum atoms are based on the assumption of $SO_2^{2\ominus}$ and $S_2^{2\ominus}$ ligands. Supporting evidence for the presence of a $SO_2^{2\ominus}$ ligand [cf. also D. M. Hoffman, R. Hoffmann, *Inorg. Chem. 20* (1981) 3543] is provided by ESCA data (very low value for $E_b(S2p_{3/2})$) and IR data (low ν(SO) value, especially in the case of **1a**, corresponding to large S–O distances; solid-state spectrum (CsI pellet) of **1**: 960, 1055 (**1a**); 1016, 1131 cm^{-1} (**1b**) [cf. R. R. Ryan, G. J. Kubas, D. C. Moody, P. G. Eller, *Struct. Bonding (Berlin) 46* (1981) 47]; the intensity of the ν(CN) band of **1b** in aqueous solution is almost as large as that of $[Mo_2^{IV}(S)_2(CN)_8]^{4\ominus}$, cf. [11]).

[2] E. Crepaz, *Gazz. Chim. Ital. 58* (1928) 391; P. Christophliemk, Diplomarbeit, Universität Göttingen 1969; M. G. B. Drew, P. C. H. Mitchell, C. F. Pygall, *Angew. Chem. 88* (1976) 855; *Angew. Chem. Int. Ed. Engl. 15* (1976) 784.

[3] Oxygen is bubbled into a solution of $K_6[Mo_2(S)_2(CN)_8]\cdot 4H_2O$ [2] **2** (2 g) in H_2O (20 mL) and glacial acetic acid (0.5 mL) for 3 h. The reddish brown precipitate is filtered off and further oxygen passed into the filtrate until a violet solution is obtained (ca. 2 h). After renewed filtration the solution is transferred to a crystallizing dish and allowed to evaporate down to ca. 5 mL in a desiccator over P_4O_{10}. After about a week the colorless byproducts are filtered off and the filtrate (covered with a watch glass) is allowed to stand for 1–2 weeks at room temperature in presence of air. The large, blackish violet crystals of **1** which separate out (ca. 0.2 g), are dried between filter papers.

[4] Space group $P\bar{1}$, $a = 1051.9(2)$, $b = 1581.6(4)$, $c = 1616.6(4)$ pm, $\alpha = 106.68(2)$, $\beta = 95.10(2)$, $\gamma = 101.61(2)^\circ$, $Z = 2$; $R = 0.061$ for 6990 independent reflections ($F_0 > 3.92\sigma(F_0)$), $Mo_{K\alpha}$ radiation, Syntex $P2_1$. The binuclear anions are grouped in pairs that are located almost parallel to each other in the crystal lattice (Mo positions of *A* and *B*: Mo1 −0.1491, 0.2770, 0.2934; Mo2 0.1209, 0.3352, 0.2983 and Mo3 0.0344, 0.2888, 0.7166; Mo4 −0.2251, 0.2227, 0.7029). The $K^\oplus$ cations are distributed over nine lattice sites of the asymmetric unit, of which three are not fully occupied.

[5] The molecular structure of diamagnetic **1b** in the $PPh_4^\oplus$ salt [C. Potvin, J. M. Brégeault, J. M. Manoli, *J. Chem. Soc. Chem. Commun.* 1980, 664] corresponds to that found here.

[6] Hewlett-Packard 5950A spectrometer, monochromatic $Al_{K\alpha}$ radiation, standard: $K2p_{3/2} = 292.2$ eV; $Mo3d_{5/2}$ 228.0 and 229.2, $S2p_{3/2}$ 163.4 ($S_2^{2\ominus}$) and 165.1 eV ($SO_2^{2\ominus}$).

[7] The addition of Na_2SO_3 provides an easy way of preventing the oxidation **1a** → **1b** by traces of oxygen, without any reduction **1b** → **1a** taking place (checked by measurements on carefully degassed solutions).

[8] F. A. Cotton, B. A. Frenz, E. Pedersen, T. R. Webb, *Inorg. Chem. 14* (1975) 391.

[9] The two complex anions could be identified on the basis of the pure diamagnetic compound $(PPh_4)_4[Mo_2(SO_2)(S_2)(CN)_8]\cdot 6H_2O$ and the $K^\oplus$ salts of **1a** (contaminated with K_2SO_4) and **1b**, now prepared by us, too.

[10] The magnetic behavior between 10 and 300 K can be described by the relationship $\chi = C/T + \chi_0$ (with $C = 0.2939 \times 10^{-5}$ m^3 K mol^{-1} and $\chi_0 = 191 \times 10^{-11}$ m^3 mol^{-1}; SI units). The Curie term of **1a** ($s = 1/2$) is determined under the formal assumption of strong antiferromagnetic interactions between the Mo atoms in the binuclear units. From its magnitude (and using $\bar{g} = 2.012$ obtained from the ESR experiment) the given composition can therefore be determined. The positive χ_0 value indicates contributions from temperature-independent paramagnetism (measurements at the Technische Hochschule Aachen).

[11] A. Müller et al., unpublished results.

[12] M. B. Robin, P. Day, *Adv. Inorg. Chem. Radiochem. 10* (1967) 247.

All-*cis*-[5.5.5.5]fenestrane**

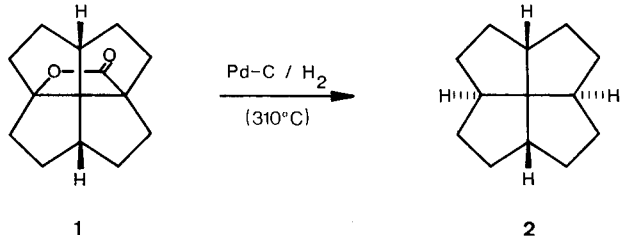
By *Marcel Luyten* and *Reinhart Keese**

Dedicated to Dr. Ulrich Weiss on the occasion of his 75th birthday

Fenestranes are of particular interest because they belong to the class of compounds which contain tetracoordinate carbon with planoid configuration[1]. We now wish to report that reductive decarboxylation of **1**[2] gave the saturated hydrocarbon **2**, the all-*cis*-[5.5.5.5]fenestrane[3,4].

Because of the specific structural properties and the steric hindrance it seemed unlikely that **1** could be transformed into **2** by typical multistep methods used for decarboxylation of lactones. In particular, ring-opening reactions, potentially leading from **1** to a γ-hydrocarboxylate or a corresponding derivative, could be excluded, because of the high tendency of lactone formation in similar cases[5].

We have now found that **1** can be reductively decarboxylated to **2** in presence of hydrogen and Pd as a catalyst[6].



1 **2**

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The structure of **2** is supported by spectroscopic data[7]. The configuration of **2** is based upon the following considerations: Of the six stereoisomeric [5.5.5.5]fenestranes[8], only the all-*cis*- and the all-*trans*-isomer, strained by 762 kJ/mol[1], have a symmetry compatible with the ^{13}C-NMR spectrum, which exhibits three lines with s, d, and t coupling patterns, respectively. Since extensive H/D exchange can be expected to take place on decarboxylation of **1** in presence of deuterium[9], it can be assumed that the all-*trans* isomer, if formed at all, should be converted into the all-*cis* isomer **2**. The capillary-GC[10] of the crude product shows—apart from **1** and solvent—only one signal; hence, it is concluded that **2**, the most stable isomer, is formed exclusively. The decarboxylation of carboxylic acids and reductive decarboxylation of lactones such as **1** is of general importance[8].

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CAS Registry numbers:
1, 69641-99-2; **2**, 67490-05-5

[1] R. Keese, *Nachr. Chem. Tech. Lab. 30* (1982) 844.
[2] R. Keese, A. Pfenninger, A. Roesle, *Helv. Chim. Acta 62* (1979) 326.
[3] According to IUPAC nomenclature [5.5.5.5]fenestrane is named tetracyclo[5.5.1.0^{4,13}.0^{10,13}]tridecane.
[4] a) [4.5.5.5]Fenestrane: W. G. Dauben, D. M. Walker, *Tetrahedron Lett. 23* (1982) 711; b) [5.5.5.5]Fenestrane-2,6,8,12-tetrone: R. Mitschka, J. M. Cook, U. Weiss, *J. Am. Chem. Soc. 100* (1978) 3973.
[5] A. Pfenninger, A. Roesle, H. Camenzind, R. Keese, unpublished results.
[6] **1** was heated to 310°C in an ampule with excess of Pd/C under hydrogen for 4.5 h. The reaction mixture, extracted with dichloromethane, consisted of **2** (90%, b.p. ca. 60°C/20 torr) and **1** (10%). In absence of hydrogen, **1** is essentially stable under such conditions.
[7] ^{1}H-NMR ($CDCl_3$): $\delta = 0.95-2.25$ (m); ^{13}C-NMR ($CDCl_3$): $\delta = 73.4$ (s), 53.6 (d), 31.1 (t); GC-MS: *m/z* (intensities [%]) = 176 (M^+, 39), 148 (100), 133 (27), 120 (44), 119 (33), 105 (35), 91 (65), 79 (54), 41 (45); molar mass by MS for $C_{13}H_{20}$: calc. 176.1565, found 176.1563; IR ($CHCl_3$): 2940, 2860, 1463, 1452, 1380 cm^{-1}.
[8] [5.5.5.5]Fenestranes can formally be constructed from subunits of *cis*- and/or *trans*-bicyclo[3.3.0]octane [1].
[9] W. F. Maier, W. Roth, I. Thies, P. von R. Schleyer, *Chem. Ber. 115* (1982) 808. These results first came to our notice subsequent to our original experiments.
[10] Conditions: a) Carbowax 20M, 20m; b) SE 54, 20m.

$[Mo_4(\mu_3\text{-}S)_4(\mu\text{-}S_2CNEt_2)_2(S_2CNEt_2)_4]$, a Compound Containing a Cubane-Like Mo_4S_4 Cluster

By *Thomas C. W. Mak, Khalid S. Jasim,* and *Chung Chieh**

Molybdenum and iron are key transition metals in nitrogenase, an enzyme responsible for nitrogen fixation. The iron may be present as Fe_4S_4 clusters, yet the state of molybdenum is still to be identified[1]. Over the years, a large number of molybdenum complexes with dithioic acids and dithiophosphates have been prepared and their structures determined, but so far only a few compounds are known to contain a cubane-like Mo_4S_4 cluster[2]. The cluster in **1** and **2** has approximate D_{2d} symmetry with only two Mo–Mo bonds of 2.862(2) and 2.881(3) Å, respectively[3]. On the other hand, the structures of the organomolybdenum compounds **3**, reported lately, contain cubane-like Mo_4S_4 clusters with six Mo–Mo bonds[4]. Recently, in our studies on molybdenum chemistry **4** was prepared, its crystal structure determined, and other properties measured. The structural analysis revealed that this compound contains a cubane-like cluster in which there are six Mo–Mo bonds. Although the present results have no direct connection with the study of nitrogenase, the existence of a cubane-like Mo_4S_4 cluster, and the unusual oxidation state of 3.5 for each Mo atom, as compared to the existence of the cluster $Fe_2Mo_2S_4$ are of considerable interest[5].

$[Mo(NC_6H_4Me)(\mu_3\text{-}S)\{S_2P(OEt)_2\}]_4$ **1**
$[Mo(NC_6H_4Me)(\mu_3\text{-}S)(S_2CN\textit{i}\text{-}Bu_2)]_4$ **2**
$[Mo(\eta\text{-}C_5H_4\textit{i}\text{-}Pr)(\mu_3\text{-}S)]_4^{n+}$ **3**, n = 0, 1, 2
$[Mo_4(\mu_3\text{-}S)_4(\mu\text{-}S_2CNEt_2)_2(S_2CNEt_2)_4]$ **4**

$Et_2N-\overset{\overset{S}{\|}}{C}-S-S-\overset{\overset{S}{\|}}{C}-NEt_2$ **5**

Brown, Glass, and *Jasim*[6] mentioned that during the preparation of $Mo_2(S_2CNEt_2)_6$ from $Mo(CO)_6$ and tetraethylthiuram disulphide **5** a black by-product was produced. We have now isolated this by-product in pure crystalline form and found that it can also be prepared by prolonged heating of the solution in the absence of light and air[7]. Complex **4** is insoluble in aliphatic and aromatic hydrocarbons, but sparingly soluble in cold acetone and chlorinated solvents. Recrystallization over more than one month from $CHCl_3$ gives square or rectangular black plates. Upon exposure to air, the crystals lose $CHCl_3$ in a few minutes (strong odor) and then disintegrate into a powder.

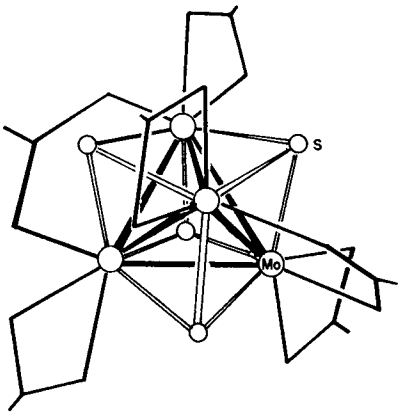

Fig. 1. The molecular structure of **4** in the crystal. For clarity, only the CS_2 groups of the dithiocarbamates are shown. The single crystal used for structure determination was kept in a chloroform atmosphere and held stationary against the wall of the capillary with petroleum jelly. Crystals of **4** are tetragonal, space group $P4_12_12$, $a = 12.442(3)$, $c = 40.30(1)$ Å and $Z = 4$; 1099, $R = 0.094$. However, the C atoms of the $CHCl_3$ and one terminal C atom of an ethyl group were not located from the difference map, and the $CHCl_3$ molecules of crystallization are randomly orientated [8].

The key features of the structure of **4** are given in Figure 1. A novel feature of the molecular structure of **4** is that it contains a cubane-like Mo_4S_4 cluster, which is similar to that of Fe_4S_4, except that all four Mo atoms are mutually bonded via single Mo–Mo bonds; in contrast, in Fe_4S_4

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there is no Fe–Fe bond. The two Mo–Mo bonds involving metal atoms bridged by $S_2CN(C_2H_5)_2$ ligands are 2.732(5) Å, slightly shorter than the other four which range from 2.858(5) to 2.870(7) Å giving an average value of 2.861(6) Å[4]. In contrast to the two short and four long Mo–Mo distances present in **4**, **3** (n = 0), has two long Mo–Mo distances (2.912(1) Å) and four short ones ranging from 2.892(1) to 2.905(1) Å (average 2.900(6) Å)[4]. Most Mo–S distances in the Mo_4S_4 cluster are close to 2.35(3) Å. The S–Mo–S angles are obtuse (101.6–107.8°) but the Mo–S–Mo angles are acute (71.5–75.2°). The molecule has a two-fold symmetry axis coinciding with that of the space group.

If the Mo–Mo bonds are ignored, the coordination geometry about each metal center is a distorted octahedron, the S–Mo–S angles being constrained by the cubane-like arrangement and by the "bite" of the chelate $S_2CN(C_2H_5)_2$ ligand. The "chelate angles" are 68.5(5) and 70.0(4)°, respectively, for angles centered at Mo1 and Mo2. Generally speaking, the Mo–S (ligand) bonds are longer than the Mo–S ("cubane") bonds, and the dithiocarbamate structural parameters are normal.

Compound **4** exhibits a single C=S stretching vibration at ca. 1000 cm^{-1} with no splitting due to a bidentate mode of bonding for the S_2CNEt_2 groups in the molecule. However, the strong bands at 565 and a shoulder at 551 cm^{-1} indicate that the C=S groups, although similar, are different, perhaps due to the inequivalence of S_2CNEt_2 groups. The Mo–S stretching bands lie between 300–360 cm^{-1}, in good agreement with the wide range of Mo–S distances in the structure.

The ^{1}H-NMR spectrum of **4**·toluene shows two triplets for the methyl groups at $\delta = 1.32$, 1.23, 1.14 and 1.29, 1.21, 1.12 ppm, respectively, in the expected intensity ratio 2:1.

The total molar magnetic susceptibility of **4**·toluene corrected for ligand diamagnetism is $\chi_m = 10.6\ m^3\ mol^{-1}$. The effective magnetic moment per Mo atom is $\mu_{eff} = 0.71\ \mu_B$, a value close to the spin-only value of two unpaired electrons. The ESR spectrum of solid **4** shows a triplet with $g_1 = 1.994$, $g_2 = 1.981$, and $g_3 = 1.977$. All these data suggest the presence of two unpaired electrons per molecule. Since the four Mo atoms are mutually bonded and their chemical states are equivalent, the unpaired electrons are not localized in any particular bond or atom, but delocalized throughout the entire cluster, in excellent agreement with the observed Mo–Mo bond lengths.

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[7] *Procedure* for **4**: A solution of 2 g $Mo_2(S_2CNEt_2)_6$ in 100 mL toluene is refluxed for 20 h. The reaction mixture is then cooled to 333–343 K, and after about 50% of the solvent was evaporated under reduced pressure black crystals were obtained by filtration. Yield 25–35%.
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BOOK REVIEWS

The Formation of the German Chemical Community (1720–1795). By *K. Hufbauer*. University of California Press, Berkeley 1982. viii, 312 pp., paperback, $ 19.45.

This volume has its origins in a dissertation published in 1970 that had already set a precedent in the history of chemistry. It deals with the astonishing ascent of chemistry in the German-speaking world from the modest status of being an adjunct to medical science to being a science "in fashion" at the end of the century in question; a change that is very difficult to explain solely in terms of the development of chemical knowledge and its practical effects. *Hufbauer* correctly seeks to probe its historical roots into a background of social structures and mentalities. The result is a fascinating case study of social, institutional and cognitive changes as scientific consequences of the enlightenment.

Rationalism and utilitarianism were the decisive arguments for the new self-confidence of the subject. Rhetoric and strategies of institutionalization marked the moulding and acceptance of the discipline. The success can be measured in the increasing material support, in the establishment of new chairs, and in the building of laboratories. In this the medical aspect waned in comparison with those impulses which chemistry received from economic and administrational sources. The education and professional careers of the eighteenth century chemists are analyzed in detail. They were first amalgamated into a German chemical community by the brilliant scientific journalist *L. von Crell*, when he created an adequate forum of communication with the prototype of a specialized scientific journal. The origins of the contributors and subscribers emphasizes the national character of the undertaking and the role of the protestant territories of central and northern Germany as the nursery of chemical science. That nationalistic motives were another basis of the alliance became evident when the chemistry of *Lavoisier* from France brought into question the very foundations of the domestic German traditions and thus fed the consciousness of a national identity, which, however, led to rather a scientific ideology then to a paradigm in *Kuhn*'s sense. The first phase of almost unanimous rejection was followed, between 1790 and 1793, by an examination of the antiphlogistic theory, whose experimentum crucis was the reaction of HgO to yield mercury and oxygen, an examination that was every

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bit as intensive as it was free from nationalistic bias. The degree of methodological agreement and the speed with which the controversy was pursued and put aside, indicate that the formation of the German chemical community had been completed by this time.

The history of this, until now, unwarrantably neglected chapter is of great general historical interest. Additionally the historian of chemistry will discover in the volume a veritable treasure trove for the history of his subject. What the 147 page appendix with biographical profiles of 65 chemists means in terms of detailed historical research can only be appreciated by those who have worked in the same field. Thereby remain some uncertainties which the abundance of chronological data concerning education and careers should not be allowed to obscure. Those who are familiar with this relatively scattered material will not be surprised. The same applies to the histories of the 59 institutions studied, for it is often impossible to conclude a great deal from the nominal incumbency of professorial chairs in the 18th century. Professorships of special subjects and courses of study did not exist in the present-day sense. For instance, under the University of Halle the too formalistic presentation results, unbelievably, in the omission of *G. E. Stahl,* the scholastic mentor of a whole generation of German chemists, simply because he formally held chairs for physiology, pathology, materia medica, botany and philosophia naturalis, but not for chemistry. Nevertheless, the priceless material contained in the appendices and footnotes, and from which by no means the last drops have been squeezed, will make the volume indispensable for future workers on the history of eighteenth century chemistry.

The reviewer would have liked to have seen more discussion of three themes. The first is the structure and peculiarities of the German academic landscape, which made possible the blossoming of the discipline on such a wide front; the second concerns the local learned societies or associations for the encouragement of industry and their part in the spreading and realization of the declared utilitarian aims of chemistry. Thirdly, the relationship of the subject to cameralism, the German form of mercantilism, should have been made plainer since the key position of chemistry in economic and financial reform was alloted to it from just this quarter. According to the cameralist theorists, chemical knowledge was an essential armament for an administrative career. This ensured public approval and support for the subject.

The reviewer is sceptical of the tendency of the presentation to attach wide-ranging labels to historical diversity. This begins with "cultural nationalism" and "national community". Just what sort of chimera could represent the German nation during the period under discussion when geographically the concept is stretched to cover both Budapest and Strasbourg as well as Graz, Kiel and Königsberg? In the cases of Greifswald (Swedish until 1815) and Kiel (Danish until 1864) there is no mention of the important consequences of the bonds with the mineralogical-analytical traditions of Scandinavian chemistry. The lasting influence of *H. Boerhaave*'s "Elementa Chemiae" is also ignored as is the increasing number of works by Scandinavian and French authors that were translated into German. If these had been included in the analysis then the social structure of the German chemical community could well have seemed less closed than it appears here. Similar remarks apply to the unspecified division into protestant and catholic territories.

The thesis that the specialist journals of *L. von Crell* moulded chemists into a close-knit, discipline-oriented, national, specialist community loses its ability to convince when it turns out later that the decisive debate concerning *Lavoisier*'s theories took place not so much in *Crell*'s "Annalen" as in the "Intelligenzblatt der Allgemeinen Literaturzeitung" which was dedicated to a much wider public.

Whether the subsequent path of chemistry was as smooth as it portrayed in the short epilogue is to be doubted. The decisive steps, however, in the formation of a scientific discipline, the breaking up of the *République des Lettres* into individual scientific communities structured along the language and subject boundaries has been pregnantly depicted by *Hufbauer* using German chemistry as an example. It is easy to criticize pioneering work. He who breaks new ground has to leave much undone. It is evidence of the superiority of this work, which is original both in subject and method, that it opens up so many questions. It will stimulate further research and already provides a wealth of material thereto.

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Hexachlorcyclohexan als Schadstoff in Lebensmitteln. Published by the Deutsche Forschungsgemeinschaft (DFG). Verlag Chemie, Weinheim 1983. 288 pp., paperback, DM 70.00.

This research report with a foreword by *H.-J. Hapke* (President of the DFG Senate Commission for the Investigation of Residues in Foodstuffs) contains 30 original contributions from two colloquia organized by this commission on November 28 and 29, 1979 and on March 6, 1980.

The title of this report seems too specialized since the volume not only contains a survey of the presence of hexachlorocyclohexane in the food *chain,* but also covers the following topics in an interdisciplinary and wide-ranging manner: historical development, manufacture, applications, properties (chemical, physical, physicochemical), analysis (including isomers in biological matrices), decomposition, transformations, residue situation and toxicology. This applies both to the insecticidally active γ-isomer (Lindane) and to the α- and β-isomers, which have attracted considerable attention in recent years.

Since the aim of the meetings was the evaluation of the material as it concerned human health, the effects of hexachlorocyclohexane isomers on the animate and inanimate human environment were not discussed.

It is particularly satisfactory, however, that not only real time monitoring (RTM) of aquatic, terrestrial, urban ecosystems and border areas was discussed but the latest experiences with the environmental specimen bank programme (ESBP), in this case the environmental bank of human samples, have also been included.

The broad disciplinary range of the 39 authors (pharmacology, toxicology, hygiene, industrial medicine, pharmacy, chemistry, food chemistry, biochemistry, ecological chemistry) and the participation of the German federal authorities and federal research institutions together with representatives of the chemical industry and international toxicological characterization and evaluation organiza-

tions should mean that this report is of interest to a much wider circle of readers than its title would lead one to suppose.

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Protein Folding and Protein Association

By Rainer Jaenicke*

Dedicated to Professor Max F. Perutz on occasion of his 70th birthday

The biosynthesis of proteins leads to linear chain molecules with a well-defined amino acid sequence that is unambiguously determined by a corresponding polynucleotide sequence at the level of the gene. The underlying mechanism of transcription and translation is based upon the complementarity of pyrimidine and purine bases, on the one hand, and the genetic code, on the other. As indicated by denaturation/renaturation experiments, the one-dimensional structural information encoded in the polypeptide chain generates a unique three-dimensional structure. In consequence, one would expect a "folding code" to exist which governs the spontaneous acquisition of the thermodynamically stable "native" structure of a given protein. The rate of folding (in vivo as well as in vitro) is fast, despite the astronomically high number of potential conformations. The mechanism of folding must therefore be kinetically controlled. Whether the native structure represents the "global" or a "local" minimum on the energy hyperspace is an open question. Above a critical size, protein molecules tend to be organized as assemblies made up of identical or non-identical subunits. The observed uniformity of a given "quaternary structure" requires a close correlation of folding and association as well as a high specificity of subunit recognition. Both are corroborated by in vitro reconstitution experiments.

1. Introduction

As indicated by their name, *proteins* are the most abundant organic molecules in cells. Due to the characteristic structure-function relationship in biomolecules, their central role in all aspects of cell structure and function is reflected by a great diversity in their spatial structure.

The conformational characteristics of each individual protein depend both on the specific sequential order of amino acids in the polypeptide chain and on the chemical environment of the molecule. The sequence is generated as the "translation" product of the corresponding homologous nucleotide sequence on the DNA. Evidently information transfer from the gene to the functional product of its expression is mediated by two "codes", the "genetic" one, which translates the m-RNA polynucleotide sequence into the linear polypeptide chain, and the "folding code", which governs the transition from the one-dimensional information contained in the amino acid sequence into the specific three-dimensional structure of an individual structural protein or enzyme.

While the genetic code has been deciphered as a degenerate triplet code with 64 combinations of 4 letters, the code of protein folding is still totally unknown. What is known is that folding occurs in a spontaneous and autonomous way without catalytic or other cellular effectors being involved. Observations corroborating this come from in vitro reconstitution experiments: the acquisition of the native structure of proteins in the course of a denaturation/renaturation cycle allows structure formation in vivo

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to be mimicked with respect to both the final product and the rate of folding[1,2].

The following discussion is based mainly on reconstitution studies, which *Max F. Perutz* has called "unboiling an egg"[3]. One reason for this approach is the fact that there is no direct way of unraveling the single steps in the folding mechanism of the nascent polypeptide chain. In addition, the free choice of variables in reconstitution experiments allows us to uncouple first-order folding reactions from second-order association reactions, thus providing a means of analyzing the correlation of subunit folding and assembly in the case of oligomeric or multimeric "superstructures".

In the following section, we shall first discuss the hierarchy of protein structure and the aims of folding and reconstitution studies; subsequent sections deal with the mechanism and kinetics of folding and association and finally with their relationship gained from in vitro experiments.

1.1. Hierarchy of Protein Structure

The term "protein folding" has come to refer to both the detailed description of the spatial arrangement (topology) of the amino acid residues in the functional protein and the mechanism or kinetics by which the unordered (nascent) polypeptide chain achieves its native conformation[4].

We shall focus on the second of these definitions. However, in order to provide a sound basis for a detailed discussion of structural transitions it may be appropriate to give a brief summary of the principles of the spatial structure of proteins[5,6].

As concluded from the vast amount of experimental data obtained from well over one hundred distinct structures of globular proteins, the three-dimensional structure of proteins may be characterized by a hierarchy of structural levels of organization[7-10].

The *primary structure*—the specific amino acid sequence along the covalent polypeptide chain—is the basic level of organization. The *secondary* and *supersecondary structures* define regular arrangements of the polypeptide backbone, e.g. helices and β structures, and their energetically and topologically preferred aggregates in terms of clusters of helices, coiled coils, βξβ units, β meanders and other preferences in β sheets etc. The *tertiary structure* refers to the three-dimensional chain fold, with structural and functional "*domains*" as spatially separated entities, sometimes with a specific function such as (allosteric) effector binding or intrinsic catalytic activity. The *quaternary structure* describes the stoichiometry and geometry of assemblies built up from subunits characterized by the foregoing levels of structural organization. Beyond a critical size of polypeptide chain, association may be considered a general structural principle, extending the molecular description into the microscopic and macroscopic range. In this structural hierarchy, "*folding*", as the transition from the one-dimensional to the three-dimensional structure, corresponds to the formation of the native secondary and tertiary structures, and "*association*" refers to the acquisition of the native quaternary structure. Both folding and association must be properly coordinated because the formation of the native quaternary structure requires that the surfaces of the structured monomers be preformed in the correct way such that specific recognition of the subunits is achieved. In fact, the specificity of association to form the native quaternary structure is exceedingly high (cf. Section 5.2).

The question as to whether folding in vivo occurs as a cotranslational or posttranslational process is still unresolved[11]. What is certain is that structural domains as well as antigenic sites are formed during translation; however, these results cannot be generalized because different systems in different compartments of the cell do not show identical patterns[11-16]. The question is essential because of the vectorial character of protein biosynthesis: if the nascent polypeptide chain acquires its biologically active form on the polysome, folding must occur stepwise from the *N*- to the *C*-terminal end. If, on the other hand, structure formation does not start until the protein is released into the cytoplasm or the lumen of the endoplasmic reticulum, folding is expected to start from the fully synthesized polypeptide chain in its random conformation. From the given alternatives, the question arises whether the products of cotranslational and posttranslational folding may differ from each other, or—to put it another way—whether the thermodynamically stable state of the native protein might be determined kinetically. There are three types of experiments which clearly indicate that the native structure of a protein molecule is determined exclusively by its primary structure (independent of its folding pathway): 1) in vitro reconstitution experiments after prior denaturation (cf. Section 3.3); 2) solid-phase peptide synthesis (from the *C*- to the *N*-terminus)[17,18]; and 3) semi-synthetic linking of protein fragments[19,20]. All three approaches seem to generate the protein in its native conformation.

1.2. Aims of Folding Studies

1.2.1. Folding Code

In view of both the "anatomy" of the known structures of globular proteins and the previously mentioned relationship between the amino acid sequence and the corresponding spatial structure of a polypeptide chain, the stage is set for elucidating the mechanisms of folding and the code by which the one-dimensional primary structure of a protein specifies its three-dimensional structure. This code will not only aid in engineering changes in protein structure (using recombinant DNA techniques), but also provide a tool to specify hypothetical functions for given amino acid sequences gained from DNA sequence analysis.

In a preliminary stage, the code of protein folding may be deduced only from small single-chain proteins. As the next step, multi-domain proteins should be included, and finally assembly systems have to be considered. Evidently with increasing size and complexity, structure predictions are complicated by the fact that both tertiary and quaternary structure are stabilized by the same types of weak intermolecular interactions[4-8,21-24].

1.2.2. Mechanism and Specificity

The formation of the native structure of proteins is strongly influenced by their aqueous or nonpolar environments (for cytoplasmic or membrane proteins, respectively). In this context, the entropic tendency to exclude water molecules from hydrophobic surfaces has three significant consequences: 1) the tertiary and quaternary structures of globular proteins favor a tightly packed state with nonpolar side chains in the interior and polar or ionized ones at the periphery of the molecule; 2) the inner "core" of the protein is unsolvated (except for very few strictly localized water molecules); 3) association leads to maximum structural complementarity of the subunit interfaces, so that all three, stoichiometry, geometry, and intermolecular interactions in a given quaternary structure, are highly specific. In order to achieve the unique fit of the subunit interfaces in oligomeric proteins, the pathway of quaternary structure formation must include well-populated, folded intermediates capable of "subunit recognition".

As in monomeric systems, where structural intermediates may be used to analyze the folding pathway, intermediates during association allow the identification of single events in the multistep folding/association process leading to oligomeric proteins. In this connection, kinetic experiments provide a means of separating both processes due to the different reaction orders of isomerization and association reactions[25,26]. By investigating the assembly pathway, we can characterize both the specificity of subunit interactions and the physicochemical and enzymological properties of kinetic intermediates. Questions that are of interest in this connection concern the structure, stability, and catalytic activity of "structured" monomers, dimers, etc., compared to the corresponding properties of the fully assembled native oligomers. For enzymes, the results may provide us with criteria for the structural prerequisites of catalytic and regulatory functions.

1.2.3. Analysis of Complex Macrostructures

Within the hierarchy of levels of protein structure, oligomeric proteins may be regarded as model systems for multimeric assemblies of higher complexity. The specificity achieved by complementarity of surface shapes, hydrophobic "patches", hydrogen bond donors and acceptors, and ion pairs is expected to hold for both oligomeric and multimeric systems. However, in many cases a detailed structural analysis of the latter is not amenable to high resolution X-ray crystallography. Oligomeric systems then may provide a key to some clearer understanding of the energetics and kinetics of association as well as the structural principles at atomic resolution.

Tobacco mosaic virus (TMV: $M_r \cong 40 \times 10^6$) may serve as an example (Fig. 1). The rodlike nucleoprotein of ca. 300 nm length and ca. 18 nm diameter consists of a single-stranded RNA-helix (ca. 6400 nucleotides) surrounded by a protein coat of ca. 2100 subunits (TMVP: $M_r = 17\,500$) [27–29]. The determination of the three-dimensional structure of the complete virion at atomic resolution has not been successful so far[27,28]. However, the RNA-free "double disc" consisting of 2×17 protein subunits turned out to be amenable to high resolution X-ray analysis[29,30]. Apart from the tertiary structure of the monomer, it provides us with certain mechanistic details of the protein-nucleic acid interaction within the virus[30,31]: only those parts of the polypeptide chain covering the RNA on the outside are found to be structured. Due to a high degree of structural flexibility of the inner part, the hole in the middle of the disc appears to be much bigger than in the whole virus.

Upon inserting the RNA, the polypeptide chain loses its flexibility, forming the rigid and highly stable nucleoprotein complex. The example illustrates the potential use of oligomeric intermediates in the structural and mechanistic analysis of complex systems; at the same time, it stresses the importance of the molecular dynamics of protein struc-

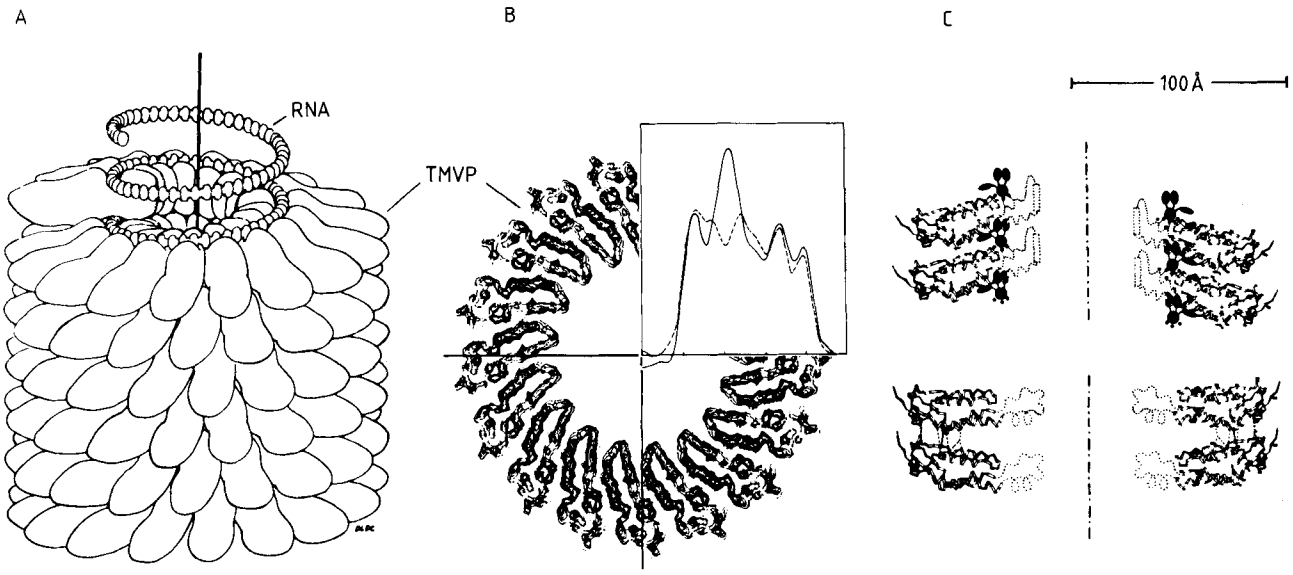


Fig. 1. Tobacco mosaic virus (TMV) as an example for a heterogeneous multimeric quaternary structure (TMVP = TMV coat protein). A) Section of about 1/20 of the length of the complete virion [27a]. B) Electron density of the double disc of TMVP and radial distribution of electron density of TMV (—) and TMVP (--) [30]. C) Side view of the TMV helix and the TMVP double disc. Dotted line: flexible part of the tertiary structure [28]. Filled circles represent the position of the RNA helix within the complete virion.

ture, which are fundamental in understanding biological function.

In the case of TMV, the double disc represents an intermediate of morphogenesis (at least in vitro): to initiate helix formation, a hair-pin loop of RNA is inserted into the double disc. "Elongation" seems to occur via (bidirectional) addition of further discs (and protein subunits) until the whole RNA strand is "coated"[32,33]. The sequential assembly reaction may be considered a model case as far as thermodynamics and kinetics are concerned[25].

With increasing complexity of the structure, an ordered assembly mechanism or specific "morphopoietic factors" may be required. This holds especially in cases where covalent modification is essential for structure formation (e.g. components of the cytoskeleton, complement system, etc.).

2. Methods

The experiments underlying the following discussion are based on the methods commonly applied to characterize macromolecules in solution (Table 1). As far as structure determination in vitro is concerned, these methods make use of the reversibility of protein denaturation focusing on *re*folding, *re*association, and *re*activation rather than folding and association. The reason is that so far no direct approach is available to study the acquisition of the native structure of the nascent polypeptide chain with sufficient resolution either in vivo or in vitro[*]. This holds especially because sensitive methods, like binding of ligands or specific antibodies, may be perturbed because the reporter molecules themselves may induce structural changes interfering with the folding process[36] (cf. Section 5.1.3).

One reason why denaturation itself is not used to unveil the structure-function relationship has previously been mentioned: dissociation and deactivation run strictly parallel (Fig. 2).

Table 1. Experimental approaches to the folding and association of proteins.

Equilibrium measurements	
State of association	Electron microscopy, ultracentrifugation, (elastic and inelastic) light scattering, gel permeation chromatography, SDS-polyacrylamide gel electrophoresis (with and without cross-linking).
Conformation	Spectroscopy (absorption, fluorescence, optical rotatory dispersion, circular dichroism, nuclear magnetic resonance), hydrogen-deuterium-(tritium) exchange, stability towards denaturation or proteolysis, binding of ligands (coenzymes, substrates, etc.) [a], chemical modification ("group specific labels")
Function (Activity)	Enzymatic assays, ligand binding (affinity chromatography)
Kinetic measurements [b]	
Assembly (Association)	Turbidity, light scattering, chemical cross-linking, hybridization
Folding	Spectroscopy (absorption, fluorescence, circular dichroism), hydrogen-deuterium exchange, limited proteolysis (Fragment analysis using gel electrophoresis), ligand binding (antibodies, allosteric effectors, etc.) [a]
Function (Activity)	Enzymatic assays, ligand binding (coenzymes, substrates) [a]

[a] Ligand binding may cause artifacts by shifting equilibria or stabilizing intermediates. [b] Depending on the time range, methods include manual mixing, stopped flow, quench stopped flow (double jump), relaxation techniques (temperature jump, pressure jump, etc.).

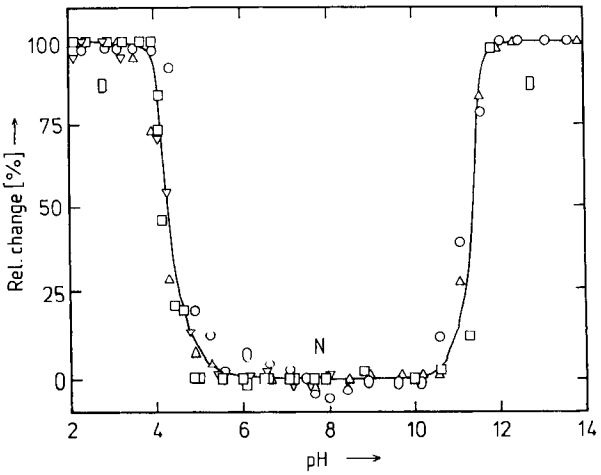


Fig. 2. pH-Dependent dissociation, denaturation, and deactivation of aldolase from rabbit muscle. N, D = native and denatured states, respectively. □ Sedimentation coefficient; △ maximum of the relative fluorescence emission ($\lambda_{exc} = 275$ nm); ▽ circular dichroism $\Theta(281$ nm); ○ specific activity [26].

Being first-order processes, they cannot be distinguished kinetically. On the other hand, the reverse reaction can be easily manipulated by varying the protein concentration, such that at low concentration the bimolecular association is rate-limiting, while at high concentration unimolecular folding gains importance. Thus, kinetic analysis allows us to gain insight into possible mechanisms of folding and association[26,37]. In order to prove or disprove such mechanisms, a variety of techniques has been devised. Determinations of the conformation and the particle distribution make use of spectroscopic methods, on one hand (absorption, fluorescence, circular dichroism, etc.), and hybridization or chemical cross-linking (e.g. with glutaraldehyde[38]), on the other (Fig. 3). Under certain conditions, intermediates of folding or quaternary structure formation may become accessible at low denaturant concentrations or by using limited proteolysis. The occurrence of such intermediates may then be used to characterize the folding pathway directly and in a detailed way[39-42]. Stability data and association enthalpies may be deduced directly from calorimetry (ΔH_{cal}) or indirectly from equilibrium constants ($\Delta H_{van't\,Hoff}$). $\Delta H_{cal} \simeq \Delta H_{van't\,Hoff}$ may be used as a criterion to prove the two-state model[43-45]. Differential scanning calorimetry has been applied successfully, especially to the study of endothermic "entropy-driven" processes[46]. In this context, measurements involving high hydrostatic pressure as well as solvation changes ("water release") may provide some deeper understanding of the thermodynamic data[23,47,48].

[*] Certain special cases (immunoglobulin [12], collagen [34], tail-spike protein of bacteriophage P22 [35]) have provided some insight into the mechanism of folding in vivo.

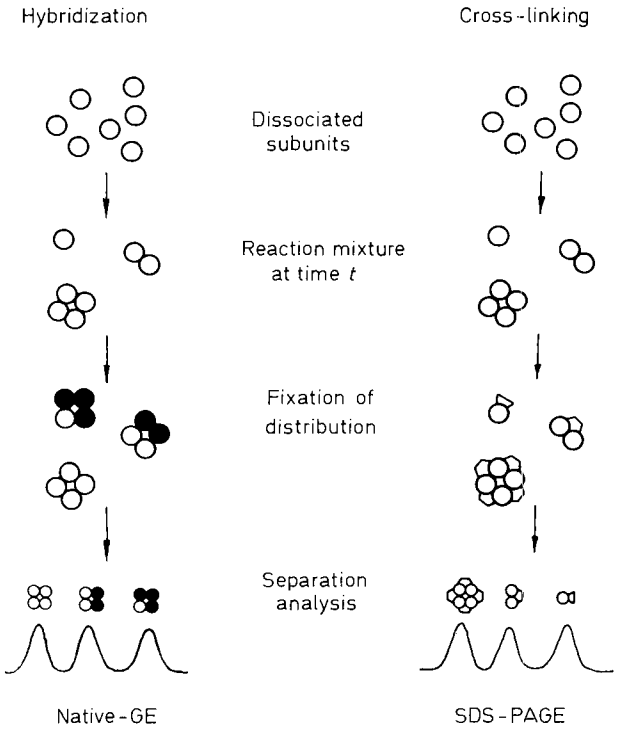


Fig. 3. Hybridization and chemical cross-linking as methods to monitor reassociation [26, 38, 115]. Native-GE = native gel electrophoresis; SDS-PAGE = SDS-polyacrylamide gel electrophoresis.

3. Nature of the Native and Unfolded States

To be able to understand the process of folding of a protein from its unordered to its active state, we have to try to describe the unfolded (D) and native (N) states. The "pathway" connecting both represents the sequence of all intermediates and transition states between D and N.

The complexity of the problem becomes obvious if we consider that "the denatured state" represents the sum of numerous heterogeneous conformations of closely similar energy which (at least in early stages of folding) belong to different folding paths. An estimate of the number of different conformations for a protein with an average molecular weight of ca. 20000 yields a figure of the order of 10^{80}[5]. Thus, the problem of the folding pathway in the sense of the previous definition is meaningless. On the other hand, the description of N and D and the characterization of intermediate states (sufficiently populated to be detectable with one of the methods mentioned) seem to be challenging, yet solvable problems[49-53].

3.1. Native State

Detailed models of the native state of proteins are obtained by X-ray analysis of crystals. Schematic representations of the "anatomy" of the polypeptide backbone[6] of a number of proteins discussed in the following paragraphs are depicted in Figure 4. Except for a certain degree of flexibility of side chains or loops in the periphery of a globular molecule, one may assume that the conformations in solution and in the crystal are identical[54,55].

Each of the topologies given in Figure 4 represents a specific way of minimizing the hydrophobic surface area, while, at the same time, forming a maximum number of stabilizing intramolecular interactions. Although the inner

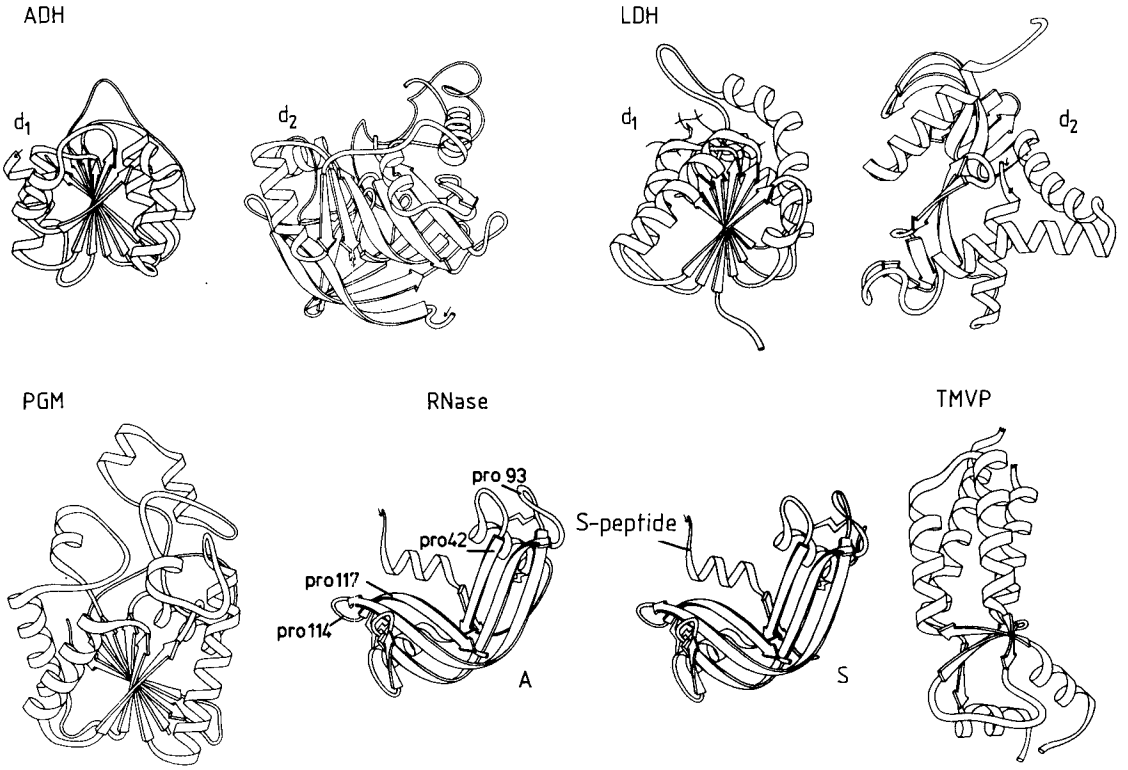


Fig. 4. Tertiary structure of selected proteins (according to Richardson [6]). ADH = liver alcohol dehydrogenase; LDH = lactate dehydrogenase; PGM = phosphoglycerate mutase; RNase = ribonuclease (RNase A includes the position of proline residues; RNase S, subtilisin-treated enzyme); TMVP = tobacco mosaic virus protein. d_1, d_2 signify the structural domains of the dehydrogenases 1 and 2, respectively.

core of the molecules resembles the crystal lattice of small amphipathic molecules with regard to the packing density and compressibility[55–57], the free energies of stabilization are small compared to the sum of the stabilizing intermolecular forces ($\Delta G_{stab} \cong 40$ kJ/mol). Clearly, the stabilizing and destabilizing contributions more or less compensate each other, so that at temperatures encountered in vivo kT is sufficient to provide the conformational flexibility required to optimize the biological function[58,59]. The size of the molecule has no significant influence on the free energy of stabilization. Domains or subunits therefore favor folding, flexibility, and transport without affecting stability.

The examples provided by NAD-dependent dehydrogenases[60] suggest that a given tertiary structure may tolerate a great number of amino acid exchanges without its topology being changed significantly ("degenerate folding code"). On the other hand, there exist only a limited number of amino acid sequences yielding a well-defined stable tertiary structure. Both observations are considered to be responsible for the surprisingly small number of "folding topologies" that have been deduced from the more than 100 crystal structures solved so far[6]. In this context, one has to keep in mind that (apart from the astronomically high number of possible conformers, ca. 10^{80} for $n \cong 170$) the 20 natural amino acids may give rise to $20^n \cong 10^{220}$ different sequences with the given chain length[*]. Clearly, there exist many "non-coding sequences" which do not generate a defined stable three-dimensional structure.

3.2. Unfolded State

The native state of a given protein requires a certain "quasi-physiological" environment. If this is changed, e.g. by varying the pH, the hydrostatic pressure, or the temperature, or by adding solubilizing agents, e.g. urea, guanidine·HCl, detergents, etc., "denaturation" occurs. In a good solvent, as a limiting case, the polypeptide chain will approach the randomly coiled state[61]. In the native state, rotation about the various bonds along the chain is restricted by the preferred trans-configuration of the peptide bond[62] and by van der Waals limitations with respect to the N–C_α and C_α–C bonds[63], which leave no more than 25% of the Ramachandran space available for attainment of the energetic optimum[*]. Part of these restrictions remain unaffected even at maximum solubilization in 6 M guanidine·HCl, so that the unfolded state may not represent an ideal random coil in the sense of the statistical theory of polymers[64,65]. Circular dichroism or (intrinsic) fluorescence may be used to measure unfolding. Both approaches clearly show that dissociation and deactivation, e.g. at acidic pH or high hydrostatic pressure, may occur without drastic changes in the native secondary and tertiary structures. Under certain experimental conditions, unfolding and dissociation may be totally "uncoupled"; the corresponding reconstitution experiments may then provide a means of studying the formation of "structured monomers" and their assembly as separate processes.

3.3. Reconstitution

For small single-chain proteins, denaturation has been shown to proceed as an equilibrium reaction

$$N \rightleftharpoons D \qquad \text{(a)}$$

where N and D are the native and the denatured states, respectively. The product of renaturation does not differ from the initial native state (Fig. 5A); the transition may be adequately described by the two-state model ($\Delta H_{cal} \cong \Delta H_{van't\,Hoff}$)[43].

Multi-domain proteins and proteins with quaternary structure usually exhibit complex behavior[26,66]: the renaturation yield is decreased, and the profiles of denaturation and renaturation do not coincide (Fig. 5B). "Wrong

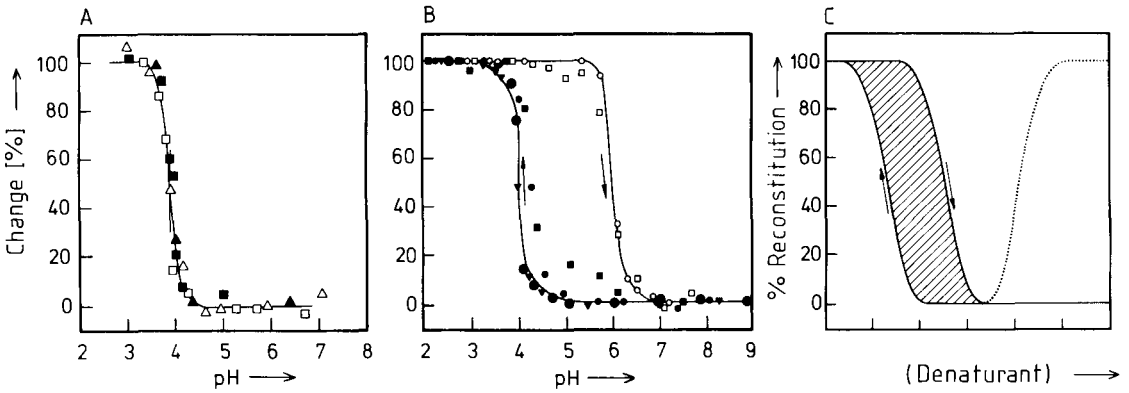


Fig. 5. Denaturation-renaturation of monomeric and oligomeric proteins [25, 26]. Open symbols: denaturation (deactivation); closed symbols: renaturation (reactivation). A) Staphylococcal nuclease: (□, ■) reduced viscosity; (△, ▲) circular dichroism Θ (220 nm). B) Lactate dehydrogenase from porcine skeletal muscle (LDH-M_4): (●) sedimentation coefficient $s_{20,w}$; (○, •) specific activity; (□, ■) maximum of relative fluorescence; (▼) circular dichroism Θ (192 nm). C) Competition of reconstitution and aggregation during the reassociation of oligomeric proteins. Hatched area: Range of metastability (aggregation) range between denaturation (↑) and renaturation (↓). The dotted curve gives the reactivation yield in the absence of the denaturant (after incubation at the given denaturant concentration) [26].

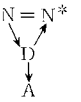
[*] An estimate of the probable number of atoms in the universe yields 10^{79} [5, 49].

[*] Crystallographic analysis has revealed that in native proteins each proline residue usually occurs as a unique *cis*- or *trans*-isomer. Release from the conformational constraint (e.g. by denaturation) yields an equilibrium distribution of *cis*:*trans*-isomers of ca. 20:80. The relaxation time of the isomerization reaction, as determined for model peptides or small proteins, varies at room temperature from seconds to a few minutes; the energy of activation is ca. 85 kJ/mol [10].

aggregation" due to intermolecular interactions of groups exposed in the N→D transition is the main reason for the observed perturbation[66–69]. For oligomeric enzymes, the inverse concentration dependence of reconstitution and aggregation (Fig. 6) clearly proves that kinetic competition prevails between the two reactions, according to

$$A \longleftarrow D \longrightarrow N^* \qquad (b)$$

where A, D, N* represent the aggregated, denatured, and reconstituted states of the protein, respectively. At high protein concentrations, aggregation governs the coupled folding-association reaction so that under unfavorable conditions "irreversible denaturation", i.e. complete aggretation, occurs[69]. The effect may easily be reversed by resolubilizing the aggregates (e.g. in 6 M guanidine·HCl) and subsequently renaturing the protein under optimum reconstitution conditions[69][*]. The final product of reconstitution (N*, after separation from A) has been shown to be indistinguishable from the initial native state N by all available physicochemical and enzymological criteria (Table 2). Thus the complete denaturation-renaturation cycle may be written as follows.



(c)

This result is crucial for two reasons: 1) the "reversibility" of denaturation corroborates the assumption that the native state is thermodynamically stable and unambiguously defined with respect to its three-dimensional structure; 2) the fact that renaturation leads back to the native state (N* = N), encourages us to consider reconstitution experiments in vitro (D→N*) as model reactions for folding and association in vivo, as far as structure, energetics and kinetics are concerned[*].

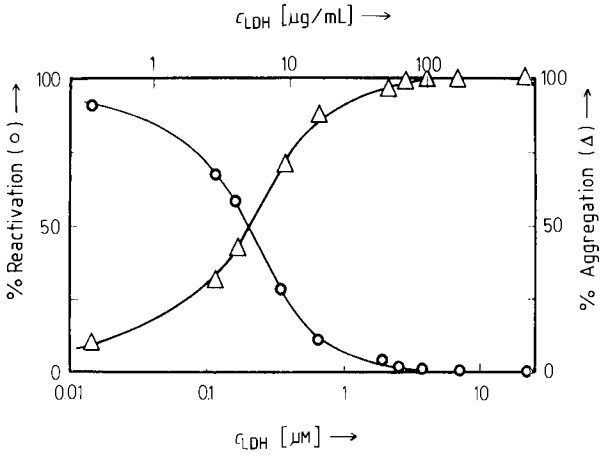


Fig. 6. Kinetic competition of reconstitution (○) and aggregation (△) for lactate dehydrogenase from porcine skeletal muscle (LDH-M_4) [69].

4. Folding

Ribonuclease may be taken as an example of the simple case of a single-chain, one-domain protein[49–53]. As derived from renaturation experiments, the half-life of the formation of the native structure is of the order of 10 s. In view of the exceedingly great number of possible conformations with a polypeptide chain of 124 amino acids, this time is extremely short. If folding implied a stochastic process, the time required to probe all possible conformations in search of the global minimum of potential energy would be about 60 orders of magnitude longer[72]. The discrepancy may be explained by kinetic and configurational constraints, defining the thermodynamically stable state as the "kinetically accessible state of minimum energy"[11]. A

Table 2. Comparison of native, denatured, and reconstituted enzymes [66, 94, 111] [a].

	ALD			LDH-M_4			s-MDH			m-MDH			ODH		
	N	D_S	N*	N	D_S	N*	N	D_G	N*	N	D_S	N*	N	D_G	N*
$s^0_{20,w}$ [S]	7.8	2.1	7.6	7.6	1.9	7.6	3.73	1.1	3.70	3.5	2.4	3.5	3.20	1.2	3.2
$M_r \times 10^{-3}$	160	40	160	140	36.5	140	67.0		69.0	68.5	35.4	70.0	45.5	44.0	
spec. activity (units/mg)	10.4	0	10.0	639	0	655	550	0	540	1040	0	1100	750	0	750
λ_{max} (nm)	319	339	319	339	336	339	332	350	332	300	302	300	327	352	
F_{rel} (%)	100	130	103	100	34	104	100	58	100	100	230	100	100	44	
$\theta_{208} \times 10^{-3}$	−14.1	−7.1	−13.7	−11.4	−10.8	−12.3	− 9.8	−6.5	− 9.8				−6.4	−3.5	
$\theta_{222} \times 10^{-3}$	−14.9	−8.5	−14.3	−15.4	−11.5	−16.0	−11.4	−0.3	−11.0				−9.6	−0.8	
K_M $(K_D)_{NADH}$ [µmol/L]				(7.4)		(8.0)	30		30	77		76	50		
$K_{M,substrate}$ [mmol/L]				0.24		0.24	0.05		0.05	0.04		0.04	1.2		1.2

[a] Enzymes: ALD = aldolase from rabbit skeletal muscle; LDH-M_4 = lactate dehydrogenase from pig skeletal muscle; s-MDH, M-MDH = cytoplasmic, mitochondrial malate dehydrogenase from pig; ODH = octopine dehydrogenase (isoenzymes A + B) from *Pecten jacobaeus*. N, D, and N* = native, denatured, and renatured states, respectively (D_S: denaturation in 1 M glycine/H_3PO_4, pH 2; D_G: denaturation in 6 M guanidine·HCl). $s^0_{20,w}$ = sedimentation constant, M_r = molecular weight, λ_{max} = maximum of fluorescence emission (λ_{exc} = 280 nm), F_{rel} = relative fluorescence. θ_{208}, θ_{222} (degrees·cm^2·dmol^{-1}) = molar ellipticity (mrw = 113) at 208 and 222 nm, respectively. K_M (K_D) = Michaelis constant, (dissociation constant) for NADH as coenzyme; $K_{M,substrate}$ = Michaelis constant for pyruvate (LDH, ODH) and oxaloacetate (MDH).

[*] Reconstitution after prior denaturation (aggregation) may be applied as a purification step in the isolation of proteins. For example, proteases may be separated from high molecular weight subunits or insoluble cellular protein by fractionation under denaturing conditions. Fractions may then become accessible after solubilization in urea, guanidine·HCl, or sodium dodecyl sulfate (SDS), etc. [69, 70].

[*] The folding of proteins with an average molecular weight $M_r \cong 100000$ takes seconds to minutes. For the total enzyme pattern, e.g. of *Escherichia coli*, the upper limit for the time required for transcription, translation, folding, and association is the generation time of the bacterium (ca. 20 min).

plausible way of most efficiently reducing the number of structural intermediates would be a unique folding pathway with stereochemically well-defined intermediates[53].

4.1. Models

"Hierarchical models" describing folding as a sequential process start from short-lived unstable microdomains and proceed via "embryos" to increasingly higher substructures. They are primarily based on short-range interactions within the folding chain. Correspondingly, such models lead to helices, (twisted) β structures or β hair-pins as intermediates; tertiary structures are then formed from these by the action of long-range stabilizing forces[73-75]. Early intermediates are assumed to be involved in isomerization equilibria favoring the less stable levels within the structural hierarchy. "Nucleation sites" may be α helices, hydrophobic clusters, antiparallel β structures (hair-pins), and β bends[74-78]. For a more detailed discussion of topological and statistical mechanical theories see [4, 53, 75].

The models of protein folding proposed so far can only claim to be of heuristic value. Experimental data are only available for phase transitions of model peptides. These data confirm the high rates observed for elementary processes such as α helix formation (ca. 10^{-6} s); for the formation of hydrophobic "clusters" (ca. 10^{-3} s) and β structures (< 1 s), only estimates can be given[49, 74].

4.2. Ribonuclease

Most theoretical studies on protein folding refer to bovine pancreatic trypsin inhibitor (BPTI, $M_r = 6500$) because of its small size. From the experimental point of view, ribonuclease (RNase, $M_r = 13\,700$) has been the most extensively studied system. Consisting of 124 amino acid residues, the enzyme has the typical size of a single folding domain. It contains all structural elements characteristic of globular proteins, including 4 disulfide bridges stabilizing the three-dimensional structure. The equilibrium of folding-unfolding U ⇌ N (Fig. 5A) fits the two-state model on thermodynamic criteria. On the other hand, the kinetics of the U→N transition are complex, requiring at least three species to fit the data quantitatively. The corresponding minimum scheme (d)

$$U_S \overset{\text{slow}}{\rightleftharpoons} U_F \overset{\text{fast}}{\rightleftharpoons} N \qquad (d)$$

can be considered as a first approximation. Stopped flow experiments allow the amplitudes as well as the kinetic constants of the two sequential steps to be determined[79, 80]

$U_S \longrightarrow N$ (80%) $\tau_{1/2} = 12$ s
$U_F \longrightarrow N$ (20%) $\tau_{1/2} = 30$ ms, 25 °C
activation energy ($U_S \rightleftharpoons U_F$): 85 kJ/mol

The relative amplitudes of the fast and slow folding species do not change at high temperatures or high denaturant concentrations; i.e. both U_S and U_F are unfolded polypeptide chains which (in the denatured state) are at equilibrium in the ratio 80 : 20. In view of the two-state situation, U_S and U_F can only differ in entropy; energetically they must be closely similar, if not identical.

These observations are consistent with the characteristics of the *cis-trans*-isomerization of X-proline peptide bonds[81-84] (cf. [*] on p. 400). A more detailed analysis of the kinetic data shows that U_S is not a homogeneous species, but rather a mixture of at least two components differing in the number and/or the position of their non-native X-proline states[85].

As mentioned previously, eq. (d) holds only in the equilibrium transition range. Under native conditions, the folding reaction $U_S \rightarrow N$ requires a more complex kinetic scheme with at least two intermediates[81, 84-86]:

$$U_S \longrightarrow I_1 \longrightarrow I_N \longrightarrow N \qquad (e)$$

Compared with the kinetics of proline isomerization in the unfolded state, I_1 is formed in a rapid reaction. It is characterized by an open conformation with a high amount of secondary structure[87]. As expected (cf. Section 4.1), this is formed at an early stage of folding[*].

I_N is a native-like intermediate with at least one "wrong" proline isomer; it contains a hydrophobic "core" and exhibits normal cytidine 2'-monophosphate (2'-CMP) binding and high catalytic activity. However, it is less stable than the native enzyme[85, 88]. Clearly, the folding of ribonuclease is not blocked by proline isomers in their non-native configuration. The secondary structure is generated in a fast reaction, preceding the formation of the native tertiary structure via I_1 and I_N. The detailed description of the folding pathway in terms of the sequential formation of defined intramolecular interactions along the polypeptide chain has not yet been obtained. In this respect, information is expected to come from folding studies involving limited proteolysis and from investigations of homologous enzymes with definite amino acid replacements. Initial results have shown that the *C*-terminal end of the polypeptide chain becomes inaccessible at an early stage of folding[42].

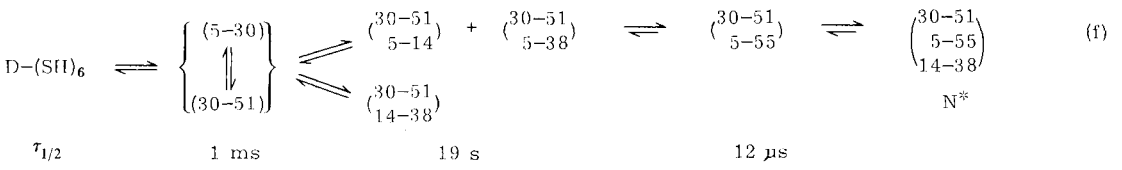
The hypothesis that folding is in principle determined by non-native proline isomers does not take into account the specific neighborhood of the proline residues within a given sequence. Energy calculations as well as folding experiments indicate that this hypothesis has to be limited to "essential" (in contrast to "non-essential") proline residues[89, 90]: Estimates of the decrease in stabilization energy induced by non-native proline residues yield a range of $\Delta\Delta G_{stab}$ between ca. 5 and ca. 85 kJ/mol, depending on the folding conditions and the position of X-proline bonds within the sequence[89]. Only those residues contributing significantly to destabilization are considered to be essential in the folding process. On investigation of homologous ribonucleases with varying proline content, neither the folding properties nor the stability of the molecules were found to be changed. Evidently the enzyme contains non-essential proline residues, and the folding pathway has

[*] Whether I_1 and N have identical secondary structures or whether a certain degree of intramolecular reshuffling occurs [73] is still unknown. A number of observations point to a close similarity.

been conserved during evolution, despite considerable alterations in the primary structure[90]. In summary, the results seem to confirm the hierarchical model of protein folding: the all-*trans* polypeptide chain synthesized on the ribosome generates, at an early stage of folding, elements of secondary structure in a fast reaction. These may be considered as "microdomains" or "embryos", which at later stages form native-like intermediates (I_1, I_N) stabilized by long-range interactions. The final product is the native enzyme (N). Additives stabilizing the native structure may accelerate the folding reaction by shifting early equilibria (e.g. $U_S \rightarrow I_1$). Clearly, the final stages ($I_1 \rightarrow N$) are not blocked by incorrect proline isomers. These are always positioned in β bends, i.e. in the periphery of the molecule, so that their *trans→cis* isomerization may occur after establishing the native-like state I_N. The flexibility of the "hinge residues" involved may serve the purpose of allowing the nascent molecule to ultimately achieve its compact native structure.

The experimental results discussed in this section were obtained using ribonucleases with unmodified disulfide bridges. As shown by *Anfinsen* et al.[91], the reduced enzyme may be completely reactivated by reoxidation. Since the cross-bridges involve cysteine residues distributed over the whole polypeptide chain, it is a plausible assumption that the formation of cystine bridges in vivo is a posttranslational event. The redox-equilibrium depends on the level of reduced and oxidized glutathione; under physiological conditions within the cell as well as in blood plasma, it is shifted towards the oxidized, i.e. the active state, of the enzyme[92].

For the trypsin inhibitor BPTI, which contains three cystine bridges, 15 different combinations of the thiol groups may occur in the reduced polypeptide[2]. In this case, careful reduction-reoxidation indicated that there exists a series of redox-equilibria on the folding pathway, such that wrong intermediates formed in preequilibria are corrected to generate finally the native state[49]. The folding pathway, showing the positions of cysteine residues involved in intermediary disulfide bonds with their respective number, may be represented schematically by eq. (f).



(f)

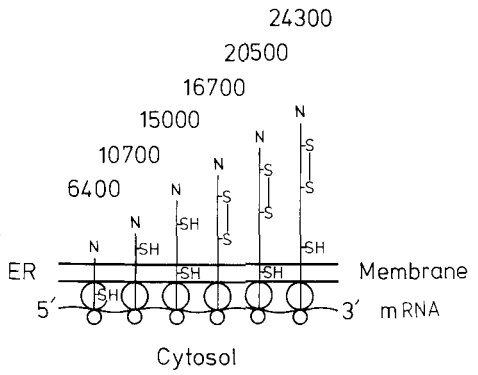


Fig. 7. Cotranslational folding of the nascent polypeptide chain of immunoglobulin. Formation of intramolecular disulfide bonds within the structural domains of the light chain of MPC 11 still fixed to the polyribosomal complex. ER = endoplasmic reticulum. The numbers refer to the molecular weight of the growing polypeptide chain (after [12]).

ments in vitro, these interactions may cause the same kind of side-reaction mentioned previously in connection with "wrong aggregation" upon subunit association (cf. Section 3.3). For this reason, the single-chain octopine dehydrogenase (as an NAD-dependent oxidoreductase, a typical multi-domain protein) exhibits a reaction yield of only ca. 70%[94]; the remaining 30% is lost due to the occurrence of incorrect intermolecular interdomain interactions[*]. The enzyme is deactivated at low guanidine concentrations in a highly cooperative monophasic process; in contrast to this simple transition, denaturation shows a biphasic profile which may be attributed to two domains, or (more probably) to the secondary and tertiary structure of the enzyme. The kinetics of renaturation also exhibit a two-step profile, since the rapid regain of native fluorescence precedes the rate-limiting reactivation, according to

$$\mathscr{M} \xrightarrow{\text{fast}} M' \xrightarrow{k_1} M \qquad (g)$$

where $\mathscr{M}$, M', and M represent the denatured, "structured", and native monomer, respectively, and k_1 is the first-order rate constant of reactivation ($k_1 = 6.6 \times 10^{-4}\ s^{-1}$).

4.3. Proteins with Domain Structure

The folding of multi-domain proteins seems to occur as a cotranslational process. For example, in vivo translation of the light and heavy chains of immunoglobulin (which is a typical multi-domain protein), clearly proves that domain folding and disulfide cross-bridge formation parallel the synthesis of each single domain[12] (Fig. 7). By making use of this kind of vectorial folding mechanism ("folding by parts"[11,93]), the nascent polypeptide chain is able to avoid wrong inter-domain interactions. In folding experiAs in the case of ribonuclease, the rapid reorganization of the secondary structure and the acquisition of the native tertiary structure follow each other.

Folding units that are integrated into the native molecule as structural domains may be considered obligatory kinetic intermediates on the pathway of folding. Apart from eliminating "wrong aggregation", they may be of se-

[*] The fact that the yield of reactivation is independent of the time of denaturation may be considered to indicate that proline isomerization in the unfolded state is not responsible for the incomplete reactivation.

lective advantage because they enhance the folding rate of long polypeptide chains ($M_r > 20000$) considerably, thus avoiding proteolytic degradation (turnover) of the nascent molecules[93].

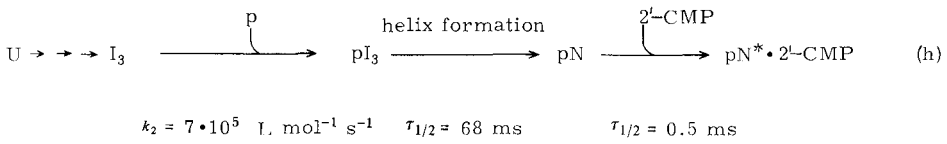
If various domains in a given molecule possess different enzymatic activities, e.g. the tetrameric aspartokinase homoserine dehydrogenase I, the local domain structure may be of additional importance because the allosteric function of the whole molecule may be used to optimize separate steps in sequential or concerted reaction mechanisms involving single domains[95]. Corresponding denaturation-renaturation experiments allow us to determine the structure-function relationship of the complex and its constituents. In this connection, the independence of domains is stressed by comparing the bifunctional complex with its proteolytically separated domains: both differ only slightly in their folding properties[96,97].

4.4. Fragments

Folding studies on protein fragments may be used to answer a number of questions: What is the minimum length of a polypeptide chain that is required for enzyme function? To what extent can separate domains or other substructures associate to form functional proteins? What is the significance of specific sequences in a given polypeptide chain for subunit assembly or for a complex reaction sequence? Can fragments be used to analyze the pathway of folding and association? At which stage in translation do folding, processing, and conjugation[*] (e.g. with carbohydrates, lipids, or nucleic acids) occur?

Fragmentation of a given polypeptide may be brought about at the level of the gene, as well as during or after translation. A few examples may serve to illustrate the alternatives: in vivo folding studies using proteins from mutants or homologous proteins from different sources differing in the sequence and length of their polypeptide chains [35, 93]; in vitro translation of manipulated structural genes, e.g. of aminoacyl tRNA synthetase (ala) which proves the "modular" organization of single activities along the polypeptide chain[98]; cotranslational cross-bridge formation between thiol groups in nascent proteins[12] (see Fig. 7); posttranslational modification applying limited proteolysis to study the folding and association of single-chain, as well as oligomeric proteins[41,42].

In studies of the correlation of folding and association, protein fragments and their reconstitution may be used as a model in two ways: on the one hand, suitable fragments may provide us with stable intermediates of folding or reconstitution which are below the limits of detection for the complete chain (cf. Section 5.3). On the other hand, the mutual effect of subunits on each other in the process of association may be simulated by applying the reconstitution of fragments. Again ribonuclease may serve as an example. The endoprotease subtilisin splits RNase A specifically, producing inactive S-peptide (p) (amino acids 1—20) and inactive S-protein (amino acids 21—124)[99]. Reconstitution of the two fragments yields a stable complex (RNase S) with full enzymatic activity (cf. Fig. 4). Under standard folding conditions, the S-peptide has a random conformation; its α-helical structure is stabilized only after reconstitution[100-102]. An analysis of the kinetics of the assembly (S-protein + p → RNase S) proves that the S-peptide binds to an early structural intermediate. However, this binding alone is insufficient to stabilize its helical conformation. It is only after the S-protein has acquired its final backbone structure that S-peptide as well as the whole complex (RNase S) are fixed in their specific active conformation. The late events in the pathway of reconstitution are summarized in eq. (h).



U, I_3, and N, N* = unfolded state, intermediate, and native states of the S-protein, respectively; p = S-peptide; k_2 = second-order rate constant of association; $\tau_{1/2}$ = half-life of transconformation.

The final product pN* exhibits properties of the native enzyme. For its recombination, the formation of the proper "recognition site" (U → I_3) is a necessary requirement. The resulting uni-bimolecular reaction sequence: *folding → association → function* provides a model for the general mechanism observed for oligomeric systems.

5. Association of Oligomeric Proteins

The model reaction discussed in Section 4 differs from the situation during folding and association of oligomeric proteins in two ways: Firstly, quaternary structure formation refers to polypeptide chains of comparable size, which in principle exceed the subdomain size, so that solvent interactions enforce a certain intrinsic backbone structure to the entities undergoing association. Secondly, subunits of oligomeric proteins (in contrast to small single-chain, one-domain systems) exhibit the previously mentioned competition between intra- and intermolecular interactions, which gives rise to incomplete reconstitution due to "wrong aggregation" (cf. Section 3.3). In consequence, the formation of "structured monomers" must precede any assembly reaction in order to achieve high yields of native oligomers (cf. Fig. 6). Specific association requires comple-

[*] Processing and conjugation specify covalent modifications of polypeptides produced by partial proteolysis and linkage of non-protein components, respectively.

mentary surface structures to be formed before subunit association occurs.

5.1. Folding and Association

In vitro reconstitution depends on the state of denaturation and the relative rates of folding and association. Because dissociation, deactivation, and denaturation of oligomeric enzymes, and the respective reverse reactions are coupled processes (Fig. 2), association cannot be totally separated from folding. Investigations of the equilibrium properties in the oligomer-monomer transition range are therefore unsuited to answering the question of whether or not isolated monomers of oligomeric proteins possess biological function or maintain at least part of the specific structural properties essential for the native state. The only way to gain insight into the correlation between folding and association is by kinetic analysis of the reconstitution reaction under a variety of folding conditions and/or starting from different stages of unfolding[37,68,91].

5.1.1. Reconstitution of Structured Intermediates

There have been successful attempts to dissociate oligomeric proteins without drastic perturbation of the native backbone structure of the constituent subunits. For the previously mentioned uni-bimolecular mechanism, this is clearly indicated by the fact that rate-limiting, first-order folding reactions become insignificant.

A few examples may serve to illustrate the wide range of approaches possible:

1) By varying the temperature, dissociation equilibria may be shifted, yielding well-defined assemblies or "structured monomers" (cf. intermediates in the endothermic polymerization of tobacco mosaic virus protein[32], cold-inactivation of enzymes[55], and other entropy-driven processes[103]).

2) High hydrostatic pressure (ca. 1 kbar) is known to induce denaturation and deactivation of oligomeric proteins, accompanied by subunit dissociation[48,55]. The complete reversibility of the reaction after decompression to normal atmospheric pressure[104–106] arises because hydrophobic side chains involved in intersubunit contact areas are reversibly buried in the interior of the subunits in the process of high pressure dissociation[106]. The exposure of charges (dissociation of ion-pairs) and their corresponding electrostrictive effect on the solvent allow the pressure-induced denaturation to be explained in terms of Braun-Le Chatelier's principle.

3) By addition of stabilizing ions (e.g. 1 M Na_2SO_4) to the denaturant, "structured monomers" may be preserved even at extremes of pH[26].

4) Dissociation by dilution (according to Ostwald's law) is expected to be the most protective approach. Evidently, it is only applicable if the dissociation constant is sufficiently high for accurate measurements to be feasible. For most oligomeric proteins this condition is not fulfilled. In addition, the reverse reaction is inaccessible to kinetic approaches. Results may therefore only be used to characterize certain equilibrium properties. In this context, the technologically important binding of proteins to a matrix is an interesting variant[107]. Using low protein concentrations, one can readily succeed in linking oligomers via single subunit contacts to the column so that denaturation-renaturation leads to separate matrix-bound monomers[108]. In certain cases, their properties were shown to resemble those of the oligomeric system. However, it appears that the matrix may "mimic" the subunit interface present in the native quaternary structure; another explanation may be the mobility of the fixed monomers due to the flexibility of the chain molecules forming the gel matrix.

5) Finally, quasi-native intermediates of association may become accessible at medium denaturant concentrations[39] or as metastable products of reconstitution[109] or limited proteolysis[110]. As shown in Section 5.3, they are highly instructive in illustrating the correlation of quaternary structure and biological function.

5.1.2. Mechanism of Reconstitution

Kinetic analyses of the concentration dependence of reactivation, renaturation, and reassociation of oligomeric proteins prove that the overall process of in vitro reconstitution is a superposition of (unimolecular) isomerization reactions with a sequence of (bimolecular) association steps according to

$$n\,M' \longrightarrow n\,M \longrightarrow \frac{n}{2}\,D' \longrightarrow \frac{n}{2}\,D \longrightarrow \frac{n}{4}\,T' \longrightarrow \frac{n}{4}\,T \longrightarrow \cdots \qquad \text{(i)}$$

Because of the "quasi-physiological conditions" commonly used in reconstitution experiments, this scheme implicitly includes three assumptions: 1) because of the stability of the native quaternary structure, reverse reactions are omitted; 2) fast folding steps preceding the formation of M′ are not included because they are not rate limiting [cf. eq. (g)]; 3) for the reconstitution of tetramers, trimers (only present in insignificant amounts) are ignored.

The strategy in evaluating the mechanism of reconstitution involves the determination of rate-limiting steps and the characterization of sufficiently populated intermediates in the given scheme. Using the time course of regaining enzyme activity and fluorescence to monitor reconstitution, one can obtain unambiguous kinetic data. Independent evidence comes from parallel cross-linking and hybridization experiments. In summary, the recovery of the native structure and function can be directly correlated with individual steps in the general scheme in eq. (i). By inspection of the kinetic reconstitution profiles, the concentration-dependent sigmoidal patterns immediately indicate that both folding *and* association are rate limiting. Both follow simple exponential functions, and concentration is a means of establishing association[26,37].

For native *dimers*, reconstitution consists of only one association step ($2M \rightarrow D'$), apart from two isomerization reactions at the level of the monomer and the dimer ($M' \rightarrow M$ and $D' \rightarrow D$). Which of these reactions is rate limiting cannot be predicted a priori. Depending on whether the formation and assembly of "structured monomers" or the reshuffling of the dimer is rate limiting, a uni-bimole-

cular or a simple unimolecular mechanism is expected to hold.

Two closely related enzymes, cytoplasmic (s-MDH), and mitochondrial malate dehydrogenase (m-MDH), illustrate the two alternatives[94, 111]. Both enzymes are synthesized in the cytoplasm as products of different nuclear genes. They are composed of identical subunits of equal size, but widely differing primary structure. Their dimeric quaternary structure is highly stable ($K_{ass} > 10^9$ L/mol) and, hence, reconstitution experiments may be performed over a wide concentration range.

Denaturation in 6 M guanidine·HCl and subsequent renaturation by dilution leads to totally different reconstitution kinetics for the two enzymes (Fig. 8). Only the fast early steps ($\mathcal{M} \rightarrow$ M′) show comparable rates. s-MDH (though chemically homogeneous) is characterized by two separable, slow, first-order reactions without any detectable concentration dependence. m-MDH, on the other hand, exhibits the typical uni-bimolecular reaction pattern. For both enzymes, the product of reconstitution is indistinguishable from the initial native state (N* = N) (Table 2).

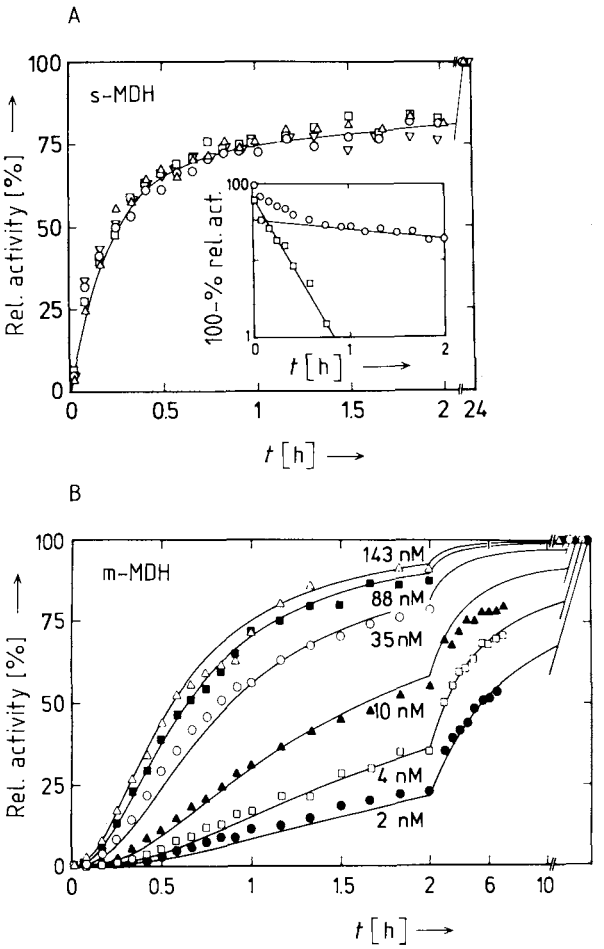
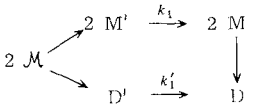


Fig. 8. Kinetics of reconstitution of dimeric porcine malate dehydrogenase (MDH) after denaturation in 6 M guanidine·HCl or 1.0 M glycine/H_3PO_4, pH 2.3. Reactivation by dilution in 0.1 M sodium phosphate, pH 7.6. For experimental details see [94, 111]. A) Cytoplasmic MDH (s-MDH). Reconstitution at c_{MDH} [μg/mL] = 1.3 (○), 3.7 (△), 6.4 (□), 12.9 (▽). Profile calculated according to eq. (j) using $k_1 = 13 \times 10^{-4}\ s^{-1}$ (68%) and $k_1' = 7 \times 10^{-5}\ s^{-1}$ (32%). Inset: linearization using 1st order kinetics to determine k_1 and k_1' (c_{MDH} = 1.3 μg/mL). B) Mitochondrial MDH (m-MDH). Reconstitution at c_{MDH} [μg/mL] = 0.07 (●), 0.14 (□), 0.35 (▲), 1.2 (○), 3.1 (■), 5.0 (△). Profile calculated according to eq. (k) using $k_1 = 6.5 \times 10^{-4}\ s^{-1}$ and $k_2 = 3 \times 10^4$ L mol^{-1} s^{-1} [111].

For s-MDH, the kinetic analysis of reactivation together with synchronous, chemical cross-linking experiments allow the following explanation of the results: The main amplitude (ca. 70%), with a half-life of ca. 9 min, represents the rate-determining folding to generate "structured monomers", which then assemble in a diffusion-controlled step ($k_2 > 10^6$ L mol^{-1} s^{-1}) to form the active dimer. The remaining ca. 30% yield the same final product with "wrong dimers" as intermediates and with subsequent reshuffling (D′ → D) as the rate-limiting step. For both pathways



(j)

reactivation and dimerization run parallel, so that neither the monomer nor folded association-intermediates can possess any significant enzymatic activity (Fig. 8 A).

The reconstitution properties of m-MDH differ from those described for s-MDH [eq. (j)]. Reactivation as well as the regain of native fluorescence are concentration-dependent, exhibiting sigmoidal kinetics (Fig. 8 B). The data may be adequately described by the above consecutive uni-bimolecular reaction scheme with one single pair of rate constants [eq. (k)]

$$2\,\mathcal{M} \xrightarrow{\text{fast}} 2\,M' \xrightarrow{k_1} 2\,M \xrightarrow{k_2} D \qquad (k)$$

The overall kinetics do not depend on the mode of denaturation (acid, urea, guanidine·HCl). Since each of these denaturants leads to a different conformational state, it is obvious that M′ must be a common structured intermediate on the pathway of reconstitution[94, 111].

In proceeding from dimers to *tetramers*, a number of new questions arise: Do intermediates of association accumulate during reconstitution? Are they catalytically active and resistant towards proteolysis? Is the dimerization of M or D the rate-limiting step in the obligatory sequential assembly pathway?

The questions may be answered using the glycolytic enzyme lactate dehydrogenase (LDH) as an example, because its three-dimensional structure is known and its reconstitution has been studied in detail[26, 37–41, 66, 68–71, 94, 104–106, 112]. Both isoenzymes, LDH-H_4 and LDH-M_4, from heart and skeletal muscle, respectively, corroborate the uni-bimolecular mechanism [eq. (i)]. For LDH-M_4 concentration-dependent reactivation kinetics yield eq. (l).

$$4\,\mathcal{M} \xrightarrow{\text{fast}} 4\,M' \xrightarrow{k_1} 4\,M \xrightarrow{\text{fast}} 2\,D \xrightarrow{k_2} T \qquad (l)$$

where $k_1 = 8 \times 10^{-4}\ s^{-1}$ and $k_2 = 3 \times 10^4$ L·mol^{-1}·s^{-1} (Fig. 9), by analogy to the mechanism obtained for dimeric m-MDH (cf. Fig. 8 B).

As shown by cross-linking experiments, dimer formation predominates in the early phase of reconstitution (Fig. 9). The corresponding decrease in monomer concentration obeys first-order kinetics with a rate constant

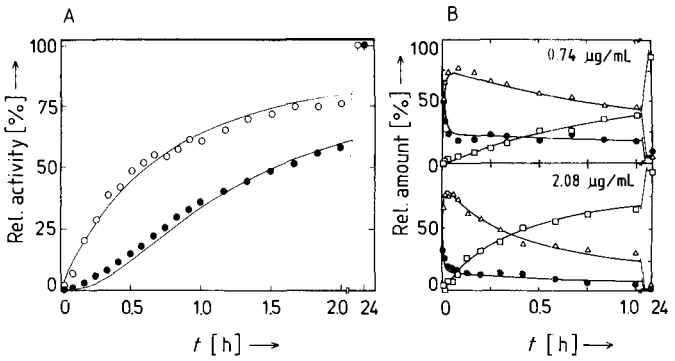


Fig. 9. Kinetics of reconstitution of tetrameric porcine skeletal muscle lactate dehydrogenase (LDH-M_4). 0.1 M sodium phosphate, pH 7.6, 20 °C. A) Reactivation after denaturation in 6 M guanidine·HCl ($c_{LDH} = 1.7$ µg/mL). Activity measured in standard assay (•). (Profile calculated according to eq. (l) with $k_1 = 8 \times 10^{-4}$ s^{-1}, $k_2 = 3 \times 10^4$ L mol^{-1} s^{-1}) and in the presence of 1.5 M $(NH_4)_2SO_4$ (○). Profile calculated with the same kinetic constants k_1, k_2, but assuming 50% dimer activity.) B) Reassociation of "structured monomers" after dissociation and deactivation in 0.1 M H_3PO_4, 1 M Na_2SO_4. Determination of the relative amount of monomers (•), dimers (△), and tetramers (□) applying SDS-polyacrylamide gel electrophoresis after chemical cross-linking with 1% glutaraldehyde. Profiles calculated according to $4\,M \overset{K}{\rightleftharpoons} 2\,D \xrightarrow{k_2} T$ with $K = 3.3 \times 10^8$ L mol^{-1} and $k_2 = 3 \times 10^4$ L mol^{-1} s^{-1}, assuming inactive monomers and dimers; the reactivation parallels tetramer formation [38, 113].

$k_1 = 8.0 \times 10^{-4}$ s^{-1}, in excellent agreement with the computer simulation of the time- and concentration-dependent reactivation profiles. The systematic deviation in Figure 9 may be explained by the fact that the dimerization of M represents a fast equilibrium reaction with $K = 3 \times 10^8$ L mol^{-1} and a rate close to that of a diffusion controlled reaction[38, 113]. Hence, the complete kinetic scheme may be described by eq. (m).

$$4\,\mathscr{M} \xrightarrow{\text{fast}} 4\,M' \xrightarrow{k_1} 4\,M \overset{\text{fast}}{\rightleftharpoons} 2\,D \xrightarrow{k_2} T \qquad \text{(m)}$$

As with monomeric and dimeric proteins, the slow M′→M transition is preceded by fast folding steps restoring ≅75% of the native ellipticity. On addition of stabilizing ions such as 1 M Na_2SO_4 to the denaturant (e.g. H_3PO_4 pH ≈ 2), unfolding may be kept to a minimum, thus giving rise to "structured monomers" (M). As expected, their reassembly obeys simple second-order kinetics with $k_2 = 3.0 \times 10^4$ L mol^{-1} s^{-1}, confirming the second rate constant in the uni-bimolecular scheme shown in eq. (l)[113].

The proposed reconstitution mechanism has been confirmed by several independent lines of evidence. 1) Reconstitution of dimeric intermediates (obtained e.g. at 1 M guanidine·HCl) yields precisely the same reactivation kinetics as observed for the monomer→tetramer assembly, thus proving that the 2 D→T transition is the rate-limiting step in the overall reactivation of LDH[39]. 2) Limited proteolysis using thermolysin during reconstitution generates artificial "stable dimers"[40]. Adding the protease at various reconstitution times again proves the dimer→tetramer transition to be rate limiting for both reassociation and reactivation. 3) Hybridization of isoenzymes at different reconstitution times enables us to calculate the concentrations of all species (M, D, and T) during reconstitution. The result confirms the mechanism given in eq. (l)[115].

A number of other tetrameric enzymes have been found to show reconstitution properties similar to those described above, so that the sequential uni-bimolecular folding-association mechanism may be considered to be the general kinetic scheme underlying the formation of the native quaternary structure[25, 26, 66, 71, 94]. In going from tetrameric to *multimeric* systems, successful attempts to achieve reconstitution of complex biological systems, such as phages, viruses, ribosomes, multienzyme complexes, etc. clearly prove that no fundamental differences occur. New facets may be a stringent assembly pathway, cooperative phenomena, and "morphopoetic factors" regulating the correct geometry and/or stoichiometry.

Three examples may illustrate the different levels of complexity.

1) *Homogeneous multimers* such as tobacco mosaic virus protein show different kinetic mechanisms depending on the mode of assembly. In this connection, the pH determines the structure with extremely high cooperativity[32, 117, 118]. Slow nucleation steps causing overshoot reactions may generate non-equilibrium states[119]. However, to a first approximation the "polymerization" may be expressed in terms of Flory's condensation polymerization [eq. (n)] using the isodesmic mechanism

$$2\,A_1 \overset{K}{\rightleftharpoons} A_2;\ A_2 + A_1 \overset{K}{\rightleftharpoons} A_3;\ A_3 + A_1 \overset{K}{\rightleftharpoons} A_4 \ldots \qquad \text{(n)}$$

where A is the polymerizing unit and K the equilibrium constant[120]. The endothermic nature of the reaction holds under all conditions which favor association. The corresponding increase in entropy is caused by release of water upon polymerization[47].

2) *Heterogeneous multimers*, e.g. multienzyme complexes, raise the question as to whether structure formation in the case of complex assemblies is an "assembly line" process with neighboring chains providing a matrix for the folding and association of other components of the multimeric system.

As with monomeric and multimeric multi-domain proteins (which are known to show independent folding of their domains[121–123]), there is no indication that multienzyme complexes require either external factors or structured components of the complex in order to accomplish proper folding. The simplest example is the tetrameric tryptophan synthase bienzyme complex from *Escherichia coli*. The two components (α and β_2) catalyze the two-step reaction shown in eq. (o).

$$\text{Indole-3-glycerol p} \xrightarrow{\text{glyceraldehyde}} \text{indole} \xrightarrow{\text{serine}} \text{tryptophan} \qquad \text{(o)}$$

"Channeling" of the common intermediate (indole) in the $\alpha_2\beta_2$ complex increases the catalytic efficiency of the partial reactions by two orders of magnitude. The α-subunit is enzymatically active; accordingly, its reactivation follows first-order kinetics. The same holds for β_2, although in this case the dimer is the active species; evidently, rate-limiting folding steps precede the diffusion-controlled assembly of the structured monomers. The reactivation of the two com-

ponent enzymes with respect to their individual activities is kinetically independent. The re-establishment of the native quaternary structure (monitored by activity and spectral analysis) obeys a complex uni-bimolecular scheme, with the increased turnover at the level of the tetramer[121, 124, 125]. Aspartate transcarbamoylase from *E. coli* (a dodecamer composed of two "catalytic" trimers (C) and three "regulatory dimers" (R)) exhibits a far more complex reconstitution pattern. The enzyme regulates the biosynthesis of pyrimidines using ATP/CTP as allosteric effectors. Both its stability and conformational flexibility depend on specific "binding domains" within the C-trimers and R-dimers, as well as between C and R. They are also responsible for the practically complete reconstitution of the enzyme after dissociation, denaturation, and deactivation.

In the concentration range 1—5 mg/mL, folding and association take a few seconds. The first step in the mechanism of reconstitution is the mutually independent folding and association of the subunits to form C and R; in a subsequent reaction both the trimeric and dimeric intermediates assemble in a heterologous fashion yielding the native enzyme ($c_6r_6 \triangleq C_2R_3$). The recombination of c_3 and r_2 (without considering homologous association) requires ten kinetic equations; it is therefore obvious that we are far removed from a definitive proof of the mechanism[126, 127].

3) *Giant molecules.* The multienzyme complex pyruvate dehydrogenase may serve as one further example. This enzyme is the connecting link between glycolysis, Krebs cycle, and fatty acid synthesis. It contains three enzyme components: pyruvate decarboxylase (E1), lipoate acyl transferase (E2), and lipoamide dehydrogenase (E3), organized as an E2 core surrounded by peripheral E1 and E3 units. The complexes from different organisms differ widely in their physical properties. The enzyme from the thermophile *Bacillus stearothermophilus,* the biggest multienzyme complex known so far ($M_r \approx 10^7$), may be only partially disassembled to functional protomers. Partial reconstitution is accomplished by means of "joint denaturation-renaturation" of the whole complex. Its time course is governed by first-order rather than second-order kinetics, thus indicating that rate-limiting folding reactions at the monomer or multimer level determine the overall mechanism of reconstitution, while bimolecular association reactions are fast. By attributing the first-order reaction to the intramolecular rearrangement ("reshuffling") of the whole complex, the mechanism shown in eq. (p) is tentatively proposed.

$$n\,M_i \xrightarrow{\text{folding}} n\,M_i' \xrightarrow[\text{fast}]{\text{association}} (M_i')_n \xrightarrow{\text{reshuffling}} N^* \qquad (p)$$

As shown in Figure 10, the folding and reactivation of the components E2 and E3 do not affect the overall reconstitution. Both are fast and independent of each other; addition of core particles (E2) during reconstitution does not alter the overall reactivation pattern[94, 128].

The fact that highly complex multienzyme systems can be reconstituted in vitro proves that even in the case of giant molecules, folding and association occur spontaneously, without necessarily requiring external factors or a specific reaction sequence. This conclusion cannot be generalized: conjugated proteins or systems as complex as ribosomes or certain phages and viruses require either "morphopoetic factors", or specific "assembly programs" to achieve their correct final structure[129–131].

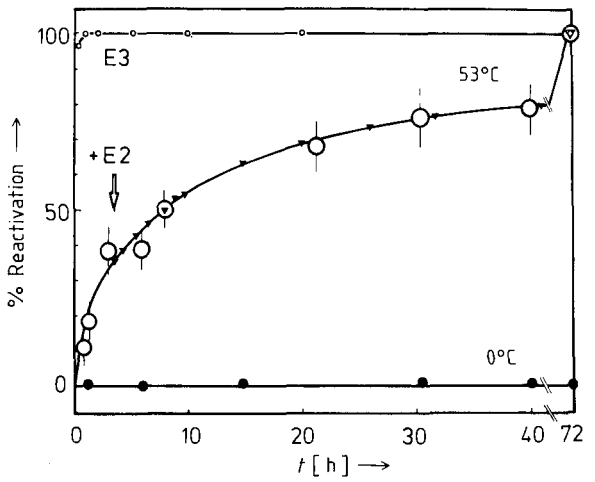


Fig. 10. Reconstitution of the pyruvate dehydrogenase multienzyme complex from *Bacillus stearothermophilus* and its components E2 (lipoate acyl transferase) and E3 (lipoamide dehydrogenase). Denaturation in 1.0 M glycine/H_3PO_4, pH 2.3. Reconstitution in 0.2 M sodium phosphate, pH 7.0, 53°C (filled circles, 0°C). ○ and the respective profile illustrate the reactivation of the complex, which is found to be independent of protein concentration in the range $40 < c_{PDH} < 160$ μg/mL. Addition of E2 at ↓ (▼) does not affect the kinetics of the overall reactivation; reactivation of E3 (○) precedes that of the complex.

5.1.3. *Ligand Effects*

Specific ligands such as cofactors, substrates, or solvent components may stabilize or destabilize the native structure of proteins. For certain enzymes, the attainment of their functional state depends on the presence, e.g., of metal ions or other ligands. In connection with the present discussion, the question arises as to whether, and at which stage, specific ligands may affect the folding and association of proteins.

In principle, effectors may influence the kinetics of reconstitution in two ways. Firstly, association of the effector with some intermediate state of reconstitution may lower the activation energy of subsequent rate-limiting steps. Secondly, binding of the effector molecule to the native or a quasi-native structure may lower the free energy of this state compared to the local minima of non-native conformations in the free energy hyperspace, in this way shifting the equilibrium towards the native structure. Thus, the effector can influence the reconstitution rate by accelerating rate-limiting steps, or by stabilizing either folding intermediates or the final product of reconstitution. Apart from the rate enhancement, both mechanisms may increase the yield of reconstitution.

In the case of NAD-dependent dehydrogenases, which have been the subject of extensive studies, the coenzyme (NAD) has often been considered as a "nucleating agent" which enhances the rate of folding and association[67]. Thorough *kinetic* analyses have shown, however, that this effect is at best small[66, 71, 111, 132] (as predicted from the high complexity of the domains involved[60]). As far as the

yield is concerned, the formation of the holoenzyme may significantly increase the reconstitution.

An example illustrating this is the effect of zinc ions on the reconstitution of liver alcohol dehydrogenase (L-ADH)[133, 134]. The ions play a double role: as a Lewis acid in catalysis and in stabilizing the structure of the dimeric enzyme. In the absence of Zn^{2+}, neither reassociation nor reactivation occur (Fig. 11). Instead, partial refolding takes place, which is easily detectable as a first-order regain of native fluorescence. Competing "wrong aggregation" is quenched immediately after Zn^{2+} is added; at the same time, enzymatic activity is recovered in a second-order reaction, which indicates that subunit assembly is required for catalytic activity.

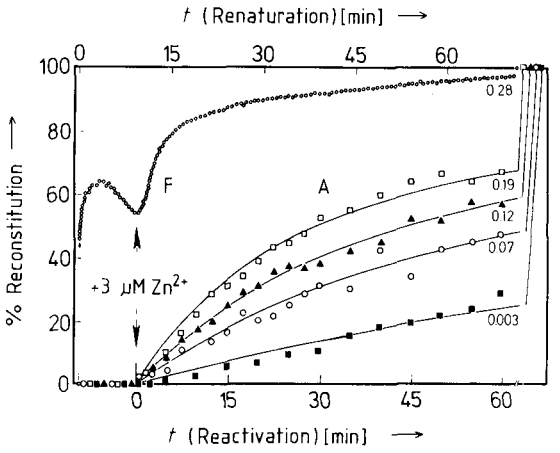
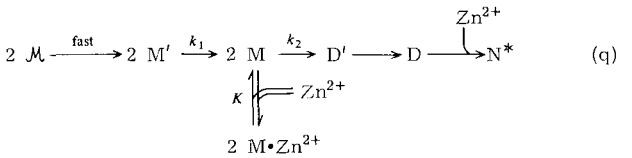


Fig. 11. Effect of Zn^{2+} and enzyme concentration on the reconstitution of horse liver alcohol dehydrogenase (L-ADH). Denaturation and subsequent removal of Zn^{2+} by gel chromatography in the presence of 6 M guanidine·HCl. Renaturation in 0.1 M sodium phosphate, pH 7.6 at 25°C, $c_{ADH} = 10$ μg/mL [0.28 μM]. F = regain of native fluorescence ($\lambda_{exc} = 275$ nm, $\lambda_{em} = 330$ nm). A = reactivation at given enzyme concentrations [μM]. Profiles calculated according to eq. (q) with $k_1 = 7 \times 10^{-3}\ s^{-1}$, $k_2 = 1.6 \times 10^3\ L\ mol^{-1}\ s^{-1}$, and $K = 0.17\ \mu L\ mol^{-1}$ [134].

Folding and association may be analyzed independently by adding Zn^{2+} after completion of the slow folding step (Fig. 11). Under these conditions, the formation of dimers (D) rather than "structured monomers" (M) becomes rate-limiting for the reactivation reaction. The kinetic scheme (q) describes the overall reaction.



(q)

At the same time, the scheme provides a plausible explanation for the antagonistic effects of Zn^{2+} at high and low concentrations: trapping of inactive monomers, on the one hand, and shifting the reaction sequence towards N*, on the other.

In summary, the example indicates a three-fold role for the ligand: participation in catalysis (as Lewis acid); fixation of folding intermediates; and stabilization of the native quaternary structure.

5.2. Specificity

The most fascinating aspect of "ligand effects" on protein folding and protein association is the specificity of subunit recognition, i.e. the question of whether or not other proteins may interfere with the formation of the native quaternary structure. The folding of a nascent polypeptide takes place in the presence of high concentrations of other proteins, including other chains coded by the same structural gene. From this fact, the question arises whether "chimeric" assemblies may exist at least as intermediates of association. Earlier negative results (which ignored the different reconstitution rates of different enzymes) did not provide an unequivocal answer[135].

The fact that closely related enzymes may form hybrids is well-established. For example, the two different polypeptide chains of the tetrameric lactate dehydrogenases LDH-H_4 and LDH-M_4 form five physiologically distinct isoenzymes, including the three hybrids H_3M, H_2M_2, and HM_3. A similar hybridization has also been observed for other enzymes. Reconstitution experiments using pyruvate dehydrogenase (Fig. 10) have shown that the individual components of the multienzyme complex are independent with respect to their folding and association kinetics. On the other hand, different enzyme complexes have been found to share certain components[94].

In order to investigate the phenomena with regard to possible kinetic intermediates or hybrid end-products, synchronous reconstitution experiments were performed using closely-related enzymes with characteristic differences in their physicochemical properties. LDH-H_4 and m-MDH (mitochondrial malate dehydrogenase) should be good candidates in this respect[60]. As shown by kinetic and equilibrium measurements, neither subunit exchange in the native state nor (intermediate) hybrid formation (LDH·MDH or $(LDH)_2 \cdot (MDH)_2$) could be detected[136]. However, these experiments are not completely unambiguous, because under the given conditions of synchronous reactivation, LDH-*dimers* as intermediates (cf. Section 5.1.2) must hybridize with MDH-*monomers*, forming trimeric hybrids. Since these are unstable, analogous experiments should be devised combining two dimeric enzymes, e.g. LDH from *Limulus* and porcine m-MDH. Both enzymes obey the same uni-bimolecular reconstitution mechanism with similar rate-constants. The outcome is precisely the same: the time course and concentration dependence, as well as the yield of reactivation in the absence and presence of the prospective partner in hybridization, remain unchanged (Fig. 12). Similarly, equilibrium measurements (using chromatographic and electrophoretic techniques) do not indicate any exchange of subunits[137].

Hence, the conclusion may be drawn that also in the case of dimeric LDH reconstitution experiments clearly disprove hybrid formation. This holds for the stable end product as well as for inactive kinetic intermediates. Evidently, the association of oligomeric enzymes is highly specific owing to complementary intersubunit binding interactions. In order to permit "recognition" of the respective interfaces, the individual subunits must not collide until they have reached a certain level of backbone structure[138]. For large subunits in vivo this requirement is presumably ful-

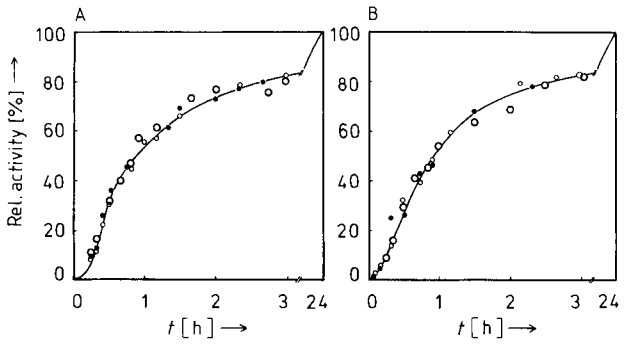


Fig. 12. Specificity of association of two dimeric dehydrogenases: Synchronous reconstitution of D-lactate dehydrogenase (D-LDH) from *Limulus polyphemus* and porcine mitochondrial malate dehydrogenase (m-MDH) [137]. A) Reactivation of 2 μg/mL D-LDH in the presence of 0.2 (•), 0.5 (○), and 1.0 (○) μg/mL m-MDH. Profile: Reactivation of D-LDH in the absence of m-MDH calculated according to eq. (k) with $k_1 = 6 \times 10^{-4}\ s^{-1}$ and $k_2 = 1.5 \times 10^4$ L $mol^{-1}\ s^{-1}$. B) Reactivation of 2 μg/mL m-MDH in the presence of 0.2 (•), 0.5 (○), and 0.9 (○) μg/mL D-LDH. Profile: Reactivation of m-MDH in the absence of D-LDH, using the kinetic constants given in Figure 8.

filled by cotranslational folding of the nascent polypeptide chain. The respective intermediate states in the folding process must be sufficiently well-defined so that even in the heterogeneous system of the cytoplasm no compartmentation is required to guarantee correct quaternary structure formation. It should be noted that the coalescence of structural domains shows a similar degree of specificity to that observed for quaternary structure formation. By analogy to the reconstitution of intact subunits, domains and/or proteolytic fragments of subunits may associate to form "nicked" assemblies which may resemble the oligomer or multimer in its functional state[93,97,110,121,122].

5.3. Structure-Function Relationship

The observation that the native structure and function of proteins does not necessarily require the full integrity of the polypeptide backbone leads back to the notion of "essential" and "non-essential residues" within a given amino acid sequence (cf. Section 4.2). In the present context, one may ask whether in the case of oligomeric enzymes the native quaternary structure is a prerequisite for catalytic function or whether intermediates of folding and association or even nicked molecules can be enzymatically active. A tetrameric enzyme such as lactate dehydrogenase is expected to provide an answer because dimeric, or sometimes even monomeric intermediates are easily accessible to structural and functional analysis.

Equilibrium data obtained from denaturation studies on a large number of oligomeric enzymes indicate that full enzymatic activity and allosteric regulation require the native quaternary structure. On the other hand, matrix-bound subunits of a number of oligomeric enzymes have been shown to be at least partially active, and certain monomeric enzymes, such as α-amylase or ribonuclease seem to exhibit allosteric properties. Kinetic experiments involving second-order steps in the reconstitution of oligomeric enzymes prove unequivocally that catalytic function requires association. Beyond the level of the dimer, additional experiments are required to determine the state of association where activity is achieved. As mentioned in Section 5.1.2, chemical cross-linking together with reactivation kinetics may provide a solution to this problem (cf. Fig. 9). Reconstitution experiments starting from well-defined intermediates of dissociation may be used as an independent method[37–40]. Attempts to solve the problem by comparing homologous enzymes with identical catalytic function but different quaternary structure were unsuccessful. For example, phosphoglycerate mutase, which occurs either as a tetramer, a dimer, or a monomer in different organisms, exhibits totally different reconstitution properties at the various levels of quaternary structure[116].

In the present context, limited proteolysis is expected to be a promising approach. Due to the non-equivalence of subunit interactions, many oligomeric enzymes may be regarded as "dimers of dimers" or "dimers of trimers" etc. For example, lactate dehydrogenase is stabilized as a "dimer of dimers" by an *N*-terminal "arm" of 20 amino acids. By cleaving off this arm using limited proteolysis during reconstitution (cf. Section 5.1.2), artificial "dimers" may be prepared that are sufficiently stable to allow detailed structural analysis.

Table 3. Comparison of native lactate dehydrogenase ($LDH\text{-}M_4$) and proteolytic "dimers" as intermediates of reconstitution [a].

	native enzyme	"dimer"
Molecular weight ($M_r \cdot 10^{-3}$)		
sedimentation equilibrium	140 ± 4	65 ± 3
gel permeation chromatography	140	70
SDS-polyacrylamide gel electrophoresis	35	34 (60%)
		18 (20%)
		12 (20%)
Sedimentation coefficient $s_{20,w}$ (*S*) [b]	7.6 ± 0.3	3.4 ± 0.2
N-terminus	acetylated	Leu, Val, Ile, Gly
Rel. fluorescence at 340 nm [$\lambda_{exc} = 280$ nm]	100	55 ± 5
Ellipticity $\Theta_{208\,nm} \cdot 10^{-3}$ [degr · cm² · dmol⁻¹]	−12.0	−11.5
Absorption $A^{0.1\%}_{280\,nm}$ [cm² · mg⁻¹]	1.4	1.8
Spec. activity [units/mg]		
standard assay	550 ± 70	2 ± 2
in the presence of 2 M $(NH_4)_2SO_4$	445 ± 65	106 ± 15

[a] Limited proteolysis using thermolysin after 1 min reconstitution. For experimental details cf. [40, 109, 110]. [b] Sedimentation analysis at $c_{LDH} = 0.2$ mg/mL; analysis of the "dimer" using activity transport [139] in the presence of 1.0–2.0 M $(NH_4)_2SO_4$.

The outcome is instructive in many respects (Table 3). Denaturation (e.g. in 6 M guanidine) and subsequent reconstitution lead back to the initial "dimer". The fact that no tetramers emerge proves that the "dimer" does not trap unmodified monomers. On the contrary, there is a high percentage of "nicking" to smaller fragments ($M_r \approx$ 12000 and 19000), reflecting the domain structure of the LDH subunits. That even the fragments retain the potential for generating the correct tertiary structure corroborates the idea that protein folding may be understood as "folding by parts" followed by "merging of domains"[111]. Clearly, the domains contain sufficient structural information (even without the connecting stretches of the polypeptide chain) to establish the specific intramolecular contacts required to stabilize the native tertiary structure[110]. Similar results have been reported for β-galactosidase, lyso-

zyme, penicillinase, tryptophan synthase, and other enzymes[140-144].

Compared with the native tetramer, the "dimer" obtained after limited proteolysis shows decreased thermal and proteolytic stability. That it binds to an NAD-specific affinity column indicates that the active center of the native enzyme must already be present at the level of the dimer, although it does not show enzymatic activity under standard test conditions. The structure must be too flexible in the dimeric state to permit catalytic activity.

This hypothesis is in good agreement with the weaker ligand affinity of the "dimer" compared to that of the tetramer. It is emphasized by the effect of stabilizing solvent conditions: after addition of "structure-making ions" such as 2 M $(NH_4)_2SO_4$ to the test mixture, up to 50% of the native tetramer activity is induced without altering the dimeric state[94, 110]. This recovery of activity is also observed for the intact dimeric intermediate on the pathway of reconstitution. If activity is measured in the presence of $(NH_4)_2SO_4$, the regain of enzymatic activity precedes tetramer formation, due to intrinsic dimer activity, and in contrast to the result obtained under standard conditions (cf. Fig. 9)[109].

In view of the structural and functional similarity of lactate dehydrogenase in its dimeric and tetrameric states, it is not surprising that the reconstitution of the $M_r \approx 34000$ subunit of the "dimer" is adequately described by the kinetic scheme given in eq. (l). By monitoring reconstitution as reactivation (with Na_2SO_4 in the enzyme assay), the overall process is determined by the same rate-limiting first-order rate constant ($k_1 = 8 \times 10^{-4}$ s^{-1}) obtained previously for the folding of the intact polypeptide chain in the reconstitution of the tetramer. By using "p" to denote the proteolytically modified chain, scheme (r) may be written:

$$2\,\mathscr{M}_p \xrightarrow{\text{fast}} 2\,M'_p \xrightarrow{k_1} 2\,M_p \xrightarrow{\text{fast}} D_p \qquad (r)$$

Comparing this scheme with eq. (l), we see that the unchanged rate constant clearly proves that the *N*-terminal "arm" is not involved in rate-limiting folding steps at the monomer level. Its functional role is the stabilization of the dimers to form the native tetramer[109]. The tetrameric quaternary structure provides optimum stability with respect to solvent parameters and turnover. At the same time, it maintains the structural flexibility required for enzyme catalysis and regulation[59, 145].

6. Concluding Remarks

We are only beginning to understand the elementary processes involved in protein folding. Thus we are still far away from unraveling the "folding code", one of the aims of systematic folding experiments and energy calculations. What has been clarified in recent years is the folding pathway of single-chain, one-domain proteins and the folding-association mechanism of oligomeric proteins in vitro.

In principle, the formation of the native, three-dimensional structure of proteins proceeds via rapidly formed structured intermediates, whose reshuffling is rate-limiting for the acquisition of the functional state.

In the case of oligomeric proteins, structure formation involves a sequence of well-defined folding and association steps. Kinetic methods have been devised to elucidate the sequential mechanism in terms of distinct unimolecular and bimolecular reactions. Such methods provide a means of determining the particle distribution during the reconstitution process, and of characterizing intermediates of association with respect to their structural and functional properties.

As a result, fast folding reactions are found to restore a considerable amount of the secondary structure. The rate-limiting process is the slow formation of correctly structured monomers, which then can associate in a highly specific way to form the native quaternary structure.

Side reactions competing with folding and association are the formation of "wrong aggregates" of partially folded subunits, on the one hand, and cotranslational or post-translational chemical modification (glycosylation, processing, etc.), on the other. The in vitro approach differs inevitably from folding of the nascent polypeptide chain in vivo with respect to the unfolded state, which may simply not exist in vivo, at least for proteins beyond a certain size. Cotranslational domain-folding may prevent the incorrect interactions which are responsible for aggregation and for slow reshuffling steps during in vitro reconstitution, thus speeding up the folding process considerably.

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Synthesis of Anti-Inflammatory α-Arylalkanoic Acids by 1,2-Aryl Shift

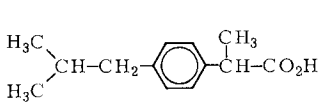
New Synthetic Methods (42)

By Claudio Giordano*, Graziano Castaldi, and Fulvio Uggeri

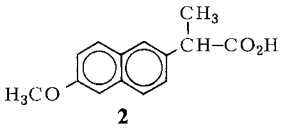
α-Arylalkanoic acids have acquired importance as anti-inflammatory agents and are now in great demand on the pharmaceutical front. Hence, the need has arisen for new and improved, economical synthetic procedures suitable for their preparation and manufacture on an industrial scale. For many years the synthetic approach to this class of compounds was restricted to the Willgerodt and Darzen reactions. More recently, several methods have been developed which are based on the 1,2-aryl shift in acetals of α-functionalized alkyl aryl ketones. This new approach starts from the oxythallation of alkyl aryl ketones first described by *Taylor* and *McKillop* in 1971. Asymmetric syntheses of some important arylalkanoic acids have also been developed on this basis. The highly toxic thallium salts may be replaced, inter alia, by catalytically effective metal salts.

1. Introduction

For almost a century, aspirin has dominated the drug armamentarium of mild anti-inflammatory, analgesic and antipyretic agents. Over the last few decades there has been a steadily increasing demand for aspirin-like drugs having higher therapeutic activity and exhibiting reduced side effects. α-Arylalkanoic acids, particularly the α-arylpropionic acids, have already proved to be suitable compounds which may fulfill these requirements[1]. In fact, some of them, like Ibuprofen **1** and Naproxen (*S*)-**2**, have already been extensively used in medical practice[1b].



1



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Most of the syntheses of α-arylalkanoic acids start from arylcarbonyl compounds[1], which can be prepared in high yields by selective electrophilic acylation and converted, by many different routes, into α-arylalkanoic acids.

Initially, the Willgerold-Kindler reaction was the method of choice to achieve this conversion[2]. Its synthetic utility is, however, limited by (a) the reaction conditions, which involve high temperatures and frequently also high pressures, (b) the tedious and rather complicated isolation technique, and (c) the yield of the products, which, in many cases, is modest and variable. Attention was then directed toward the Darzens reaction[3], i.e. the base-promoted condensation of an aldehyde or a ketone with an α-halo ester to give an α,β-epoxyester, which, in turn, is converted by a multistep process into the desired acid.

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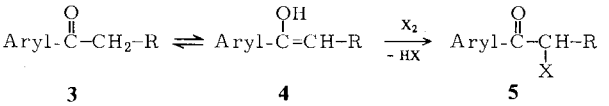
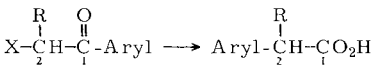
Subsequently, more convenient syntheses of α-arylalkanoic acids were found, based on the rearrangement of α-halo, α-thallio(III), α-tosyl, or α-diazoalkyl aryl ketones **5**.



3 **4** **5**

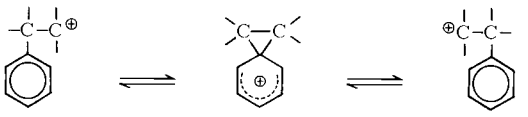


5 **6**

In general, these processes are characterized by two fundamental steps: a) attack of an electrophile on the enol form **4** of the non-functionalized ketone **3**; b) rearrangement of the α-functionalized ketone **5** thus obtained to the acid **6**.

Since the first step can be accomplished in many convenient ways, the success of the synthesis is mainly determined by the factors which govern the 1,2-shift of the aryl moiety.

In principle, 1,2-aryl shifts can occur with β-arylalkyl cations[4], β-arylalkyl radicals[5], β-arylalkyl carbanions **7**, **8** and **9**[6], and β-arylalkyl carbenes[7] (with these last substrates, however, the reaction is not general and occurs with very low selectivity, since hydrogen migration prevails over aryl migration). In all cases it has been established that the process is intramolecular.



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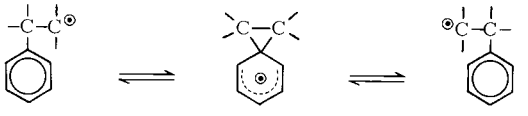

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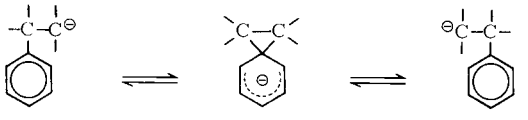


9

For the synthesis of α-arylalkanoic acids, the rearrangement of β-arylalkyl cations such as **11**, derived from α-functionalized alkyl aryl ketones **5**, is undoubtly the most interesting of these possibilities. In fact substrates having the correct oxidation state give directly the carboxylic acids derivatives, whereas the rearrangement of free radicals or carbanions has to be followed by oxidation.

The participation of the aryl group in the electrophilic rearrangement of β-haloarylalkanes is well established: Electron-withdrawing groups decrease and electron-donating groups increase the reaction rate[8].

Molecular orbital calculations carried out for the benzenium ion $C_6H_7^{\oplus}$ using EHT, CNDO/2, and ab initio methods also support participation of the aryl group. It has been concluded[9] that CNDO/2 overestimates the stability of cyclic structures (the energy of **10** is 119.4 kcal/mol lower than that of **11**), whereas EHT underestimates the stability of the cyclic structures (the energy of **11** is 20 kcal/mol lower than that of **10**). Ab initio calculations[10] with a contracted STO-3G basis set indicated that the bridged structure **10** is more stable, by 35—50 kcal/mol, than any possible conformations of the open chain species **11**.

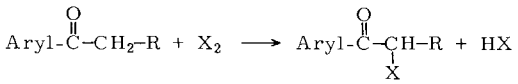
10 **11**

When a carbonyl group replaces the benzylic methylene group in the substrate, 1,2-migration of the aryl group should be less favored, since the geometry of the sp^2 carbonyl carbon "resists" the attainment of the spiro, cyclopropyl-like transition state[11]. However, the favorable sp^3 geometry of the benzylic carbon can be easily restored by masking the carbonyl group as an acetal, which, destabilizing the incipient carbenium center, should favor participation of the aryl group[8].

Accordingly, in all the successful synthetic applications of this strategy the masking of the carbonyl group as an acetal has been the expedient to obtain the desired 1,2-aryl migration.

2. Rearrangement of α-Haloalkyl Aryl Ketones

Halogenation is an inexpensive and simple way to functionalize alkyl aryl ketones **3** in the α-position to give **5**. However, solvolysis of phenacyl halides such as **12** leads only to the substitution products **13**[12]; all attempts to obtain rearrangement products remained unsuccessful[12].



3 **5**

12 **13**

Instead, in the silver-ion assisted solvolysis of α-halobenzyl aryl ketones and of α-halo-*tert*-alkyl aryl ketones a 1,2-shift of the aryl group was observed. In most cases substitution or elimination reactions[13-15] occurred together with the rearrangement.

In the silver ion-assisted methanolysis of α-bromo-*prim*- and α-bromo-*sec*-alkyl aryl ketones **14** both substitution (formation of **15**) and rearrangement (formation of **16**) occur, and the ratio **16/15** is strongly affected by the acidity of the reaction medium[16]. The 1,2-aryl shift is favored by electron-donating substituents on the aryl group (Table 1).

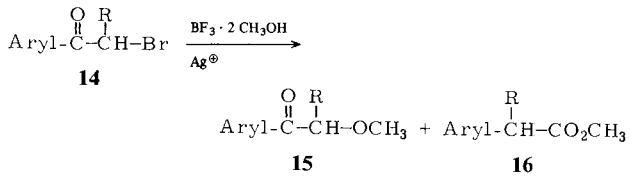
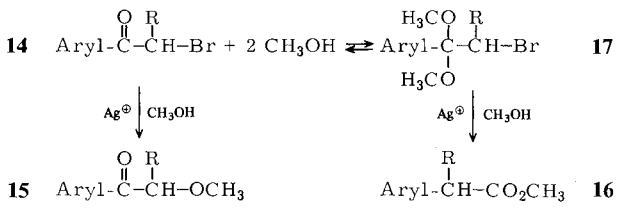


Table 1. Reaction of the ketones **14** to give **15** by substitution or to give **16** by 1,2-aryl shift; influence of substituents in the aryl group.

Aryl	R	Yield [%] 15	16	16/15
4-Methoxyphenyl	H	11.6	58	5
Phenyl	H	40	8	0.2
4-Methoxyphenyl	CH_3	8.7	78	9
Phenyl	CH_3	25.5	51	2
6-Methoxy-2-naphthyl [a]	CH_3	5.7	85	15

[a] Methyl ester of **2**.

When the rearrangement of 2-bromo-4′-methoxyacetophenone (R = H, Aryl = 4-methoxyphenyl) was carried out in CD_3OD, ^{1}H-NMR analysis revealed the presence of the starting ketone, the corresponding enol ether, and the acetal **17**[16b]. This observation suggested that the acetal was responsible for the rearrangement product.



In order to verify this hypothesis, acetals of α-halo-*prim*- and α-halo-*sec*-alkyl aryl ketones were reacted with silver salts in methanol[11]: quantitative yields of rearrangement products were obtained (Table 2).

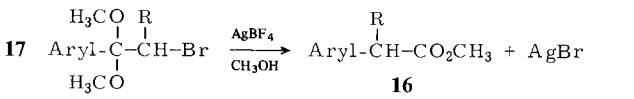


Table 2. Reactions of the acetals **17** with $AgBF_4$ in methanol involving 1,2 aryl shift to give **16** and AgBr.

Aryl	R	t [h]	Conversion [%]	Yield [%]
4-Methoxyphenyl	H	2	95	98
4-Methylphenyl	H	6	85	98
3-Chlorophenyl	H	48	17	98
4-Methoxyphenyl	CH_3	1.5	96	98
6-Methoxy-2-naphthyl [a]	CH_3	1	98	98

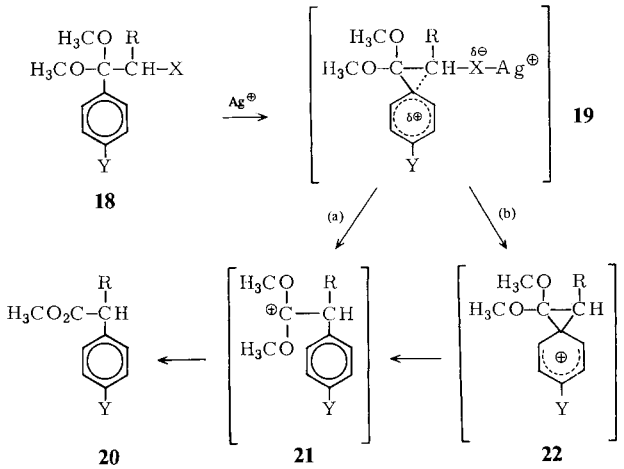
[a] Methyl ester of **2**.

Kinetic investigations revealed that the reaction is first-order in $AgBF_4$ and in the α-bromo acetal **17**, indicating that the rate-determining step is the interaction between **17** and $Ag^{\oplus}$.

A good Hammett correlation between σ^+ of the substituents and the corresponding rate constants was found ($\rho = -3.29$). Thus, the rearrangement is strongly influenced by the polar character of the substituents.

This behavior contrasts with the silver ion-assisted ethanolysis of phenacyl bromides[12a], where only substitution products (ethers) are formed and the reaction is insensitive to the substituents on the phenyl ring. This explains the effect of the substituents on the product pattern when the acetal is in equilibrium with the ketone: the rate of substitution of the ketones is not affected by the substituents in the aromatic ring, whereas the rearrangement rate of the acetals strongly increases with the electron-releasing ability of the groups present on the phenyl ring.

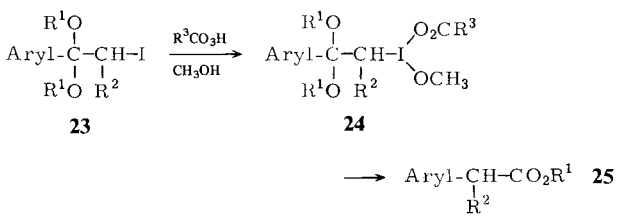
The strong polar effect found in the rearrangement of α-bromo acetals indicates that in the transition state the aryl group assists the development of the positive charge on the α-carbon. Moreover, the order of reactivity of the α-halo acetals (I > Br > Cl) is that expected on the basis of the carbon-halogen bond energies, showing that this bond is broken in the rate determining step. A reaction mechanism based on the above observations is depicted in Scheme 1.



Scheme 1.

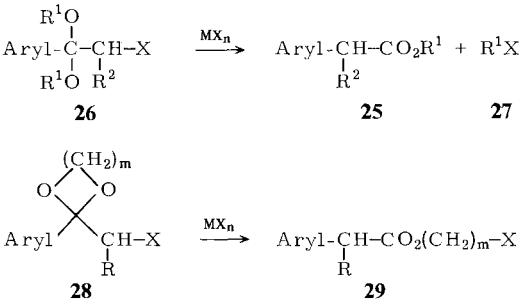
Depending upon the electron density on the aryl ring, the reaction of the acetal **18** via **19** to the cation **21** proceeds either via a synchronous pathway (a) (Y = electron-withdrawing group) or through pathway (b), which involves the intermediacy of **22** (Y = electron-releasing group).

The use of stoichiometric amounts of silver salts makes the method less attractive for large-scale preparation and unsuitable for industrial processes. Therefore, a large effort was devoted to overcoming the synthetic limits related to the use of silver salts. To this end, α-iodo acetals **23** were oxidized by peracids to iodine(III) derivatives **24**; these compounds rearrange spontaneously to **25**, since the iodine(III) species are very good leaving groups[17].

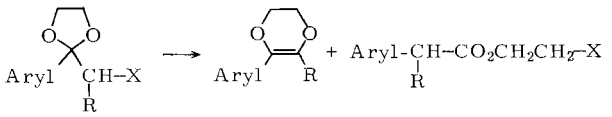


Very recently, *Thomas* and *Higgins*[18] have used the same approach and obtained similar results. These authors also reported[18] that all attempts to promote the rearrangement of α-halo acetals with a variety of Lewis acids had failed. However, under appropriate experimental conditions[19,20], acidic catalysts ("soft and borderline" Lewis acids) that—like the silver ion—are capable of polarizing to some extent the carbon-halogen bond of α-haloalkyl aryl acetals and have a poor affinity for the oxygen atoms of the acetal, lead to the desired rearrangement.

Actually, zinc, tin, copper, mercury, palladium, cobalt, antimony, bismuth, and iron salts were found to promote the conversion of alkyl acetals of α-haloalkyl aryl ketones **26** into alkyl esters of α-arylalkanoic acids **25** and into alkyl halides **27**; several solvents, including hydrocarbons, were used[20]. With cyclic acetals **28**, ω-haloalkyl esters **29** were formed.



Generally, in reactions involving ethylene acetals of α-halo-*sec*-alkyl aryl ketones **28a** devoid of electron-donating substituents on the aryl ring, sizeable amounts of 5-alkyl-6-aryl-2,3-dihydro-1,4-dioxin **30** besides **29a** were formed as a result of the oxygen migration[21].



Classical Lewis acids, such as aluminum trichloride and boron trifluoride, and, in general, "hard" acids are less effective toward the rearrangement because they strongly complex the oxygen atoms of the acetal group, favoring the conversion of the acetal into the corresponding ketone or enol ether. Some significant results, including those related to commercially important compounds, are listed in Table 3.

The main advantage of this method is the use of merely catalytic amounts of inexpensive metal salts. Accordingly, it has been the method of choice for the manufacture of some α-arylpropionic acids on an industrial scale.

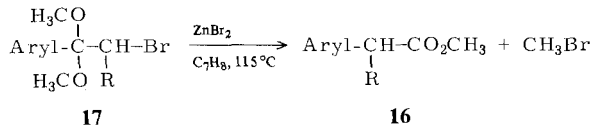
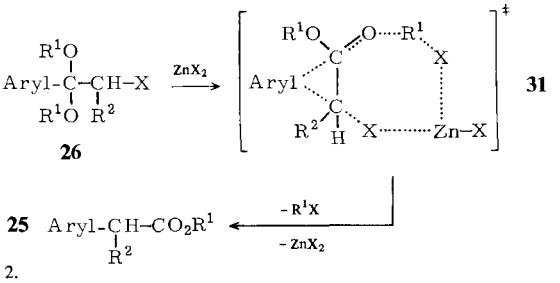


Table 3. $ZnBr_2$-catalyzed reaction of the acetals **17** in toluene at 115 °C with 1,2-aryl shift to give **16**.

Aryl	R	*t* [h]	Yield [%]
4-Methoxyphenyl	H	1	95
4-Methylphenyl	H	8	80
4-Methoxyphenyl	CH_3	0.5	98
4-Methylphenyl	CH_3	1.5	96
4-Chlorophenyl	CH_3	24	78
6-Methoxy-2-naphthyl [a]	CH_3	0.5	98
4-Isobutylphenyl [b]	CH_3	4	94

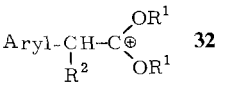
[a] Methyl ester of **2**. [b] Methyl ester of **1**.

Investigations on the mechanism of the reaction proved that the role of "soft and borderline" Lewis acids parallels that of silver salts in promoting the 1,2-aryl shift (Scheme 2).



Scheme 2.

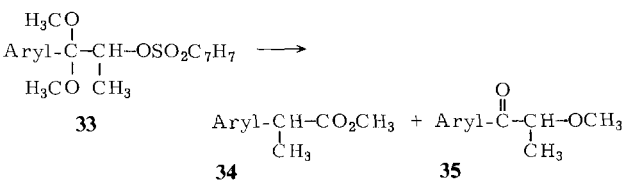
The interaction between the substrate and the catalyst causes a progressive polarization of the carbon-halogen bond with concomitant migration of the aryl group to give **31** as a possible transition state. The conversion of the transition state **31** into the products can be either a synchronous or a two-step process via cation **32**.



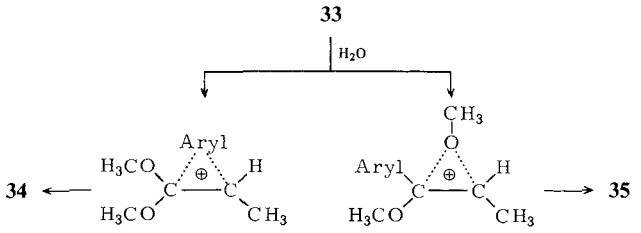
More recently it has been reported that acetals of α-haloalkyl aryl ketones **26** rearrange to esters of α-arylalkanoic acids **25** when heated in polar protic solvents under neutral conditions *in the absence of metal catalysts*[22,23].

3. Solvolysis of the Acetals of 1-Aryl-2-sulfonyloxy-1-alkanones

Solvolysis of the acetals of 2-tosyloxypropiophenones **33** in aqueous methanol in the presence of a weak base furnishes methyl α-arylpropionates **34** and 2-methoxypropiophenones **35**[24].

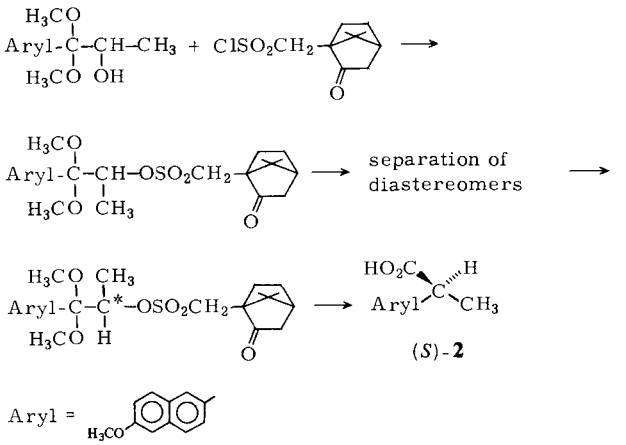


Formation of **34** and **35** has been ascribed to an intramolecular displacement of the tosyloxy group by the neighboring aryl and methoxy group, respectively.



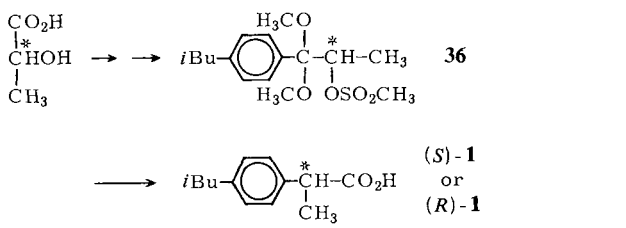
The polar effect of the substituents on the aryl group in CH_3OH/H_2O has been studied; it has been found that both the rate and the selectivity of the reaction towards ester formation are enhanced on increasing the electron density on the aromatic ring.

This method has allowed the direct synthesis of one specific enantiomer of α-arylalkanoic acids by rearrangement of an optically pure α-sulfonyloxy acetal[25]. This result is important, because it has been found that for some α-arylalkanoic acids only one enantiomer exhibits a high anti-inflammatory activity. A well-known example is that of 2-(6-methoxy-2-naphthyl)propionic acid **2**, whose *S*-isomer (Naproxen) is 28 times as active as the *R*-isomer. Naproxen has been synthesized according to the reaction sequence outlined in Scheme 3.



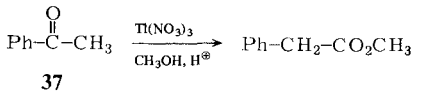
Scheme 3.

It is worth emphasizing that the 1,2-rearrangement proceeds with 100% inversion of configuration, consistent with a S_N2 mechanism. On this basis, an asymmetric synthesis of α-arylalkanoic acids, e.g. the enantiomers of **1**, has been developed[26]; it involves the intermediacy of an enantiomerically pure acetal **36**, obtained in a multistep process from lactic acid (*R* or *S*).



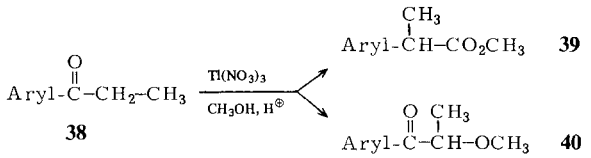
4. Reaction of Alkyl Aryl Ketones with Thallium(III) and Lead(IV) Salts

A direct method for converting alkyl aryl ketones into esters of α-arylalkanoic acids by thallium(III)-promoted rearrangement was first reported by *McKillop, Swann,* and *Taylor* in 1971[27]. This oxidative rearrangement of alkyl aryl ketones is a smooth reaction[28]. Acetophenone **37**, for instance, is rapidly converted into methyl phenylacetate with thallium(III) nitrate in acidic methanol at room temperature.

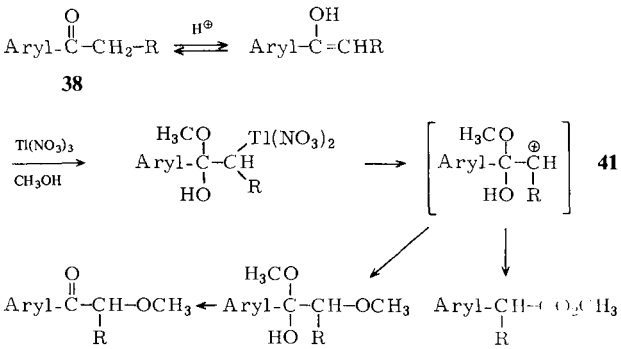


However, acetophenones having the aromatic ring deactivated by electron-withdrawing groups react slowly, giving methyl arylacetates in low yields.

With propiophenones **38** a mixture of products is obtained, among which the expected esters **39** and α-methoxypropiophenones **40** are the major components.



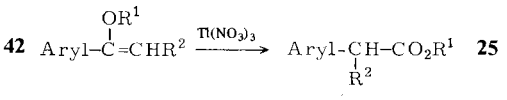
The reaction mechanism is shown in Scheme 4: the individual steps are acid-catalyzed enolization of the ketone **38**, oxythallation of the C=C bond thus formed, and oxidative rearrangement by 1,2-aryl migration with simultaneous reduction of thallium(III) to thallium(I). The substantial amounts of α-methoxy derivatives found in the case of propiophenones were explained by the authors in terms of an increased stabilization of the cation **41** by the methyl group (R = CH_3).



Scheme 4.

Later on, the use of thallium(III) nitrate in trimethyl orthoformate/methanol[29] or of "anhydrous thallium(III) nitrate" (adduct with $3CH_3OH$) on a solid support[30] al-

lowed high conversion of propiophenones into esters of α-arylalkanoic acids, with the virtual exclusion of α-methoxy derivatives. The results of this study suggested that in trimethyl orthoformate the reaction might proceed via oxidation of the enol ether formed in situ. In agreement with this prediction, it was found[31] that enol ethers **42** undergo rearrangement with high selectivity to the esters **25**.



More recently, the mechanism of oxythallation of alkyl aryl ketones was further investigated by *Thomas* and *Higgins*[18,32]. In spite of some minor discrepancies, all authors agree that the rearrangement products stem from α-thallated hemiacetals or acetals, whereas the substitution products (i.e. α-alkoxy derivatives) are formed from α-thallated ketones. This conclusion emphasizes the close similarity between this rearrangement and that of α-haloalkyl aryl ketones.

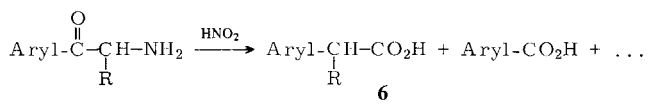
Two main aspects limit the industrial development of this synthesis: the cost of the thallium salts and their toxicity. Successful studies have been reported on the use of oxidants capable of regenerating the thallium(III) species in a continuous process[33]. Nevertheless, besides the technological problems involved in the production, doubts remain as to whether government authorities would permit the use of drugs manufactured via a thallium-based route.

Many efforts have been made to avoid the use of thallium salts. For instance, the reaction between alkyl aryl ketones and lead(IV) acetate has been investigated[34,35]. The results resemble those obtained with thallium(III) compounds, and the mechanism seems to involve the rearrangement of an α-oxyplumbated hemiacetal.

Esters of α-arylalkanoic acids have also been obtained by reacting α-haloalkyl aryl ketones and thallium(III) nitrate in the presence of trialkyl orthoformate[36]. In this case the thallium(III) salt probably acts as a Lewis acid.

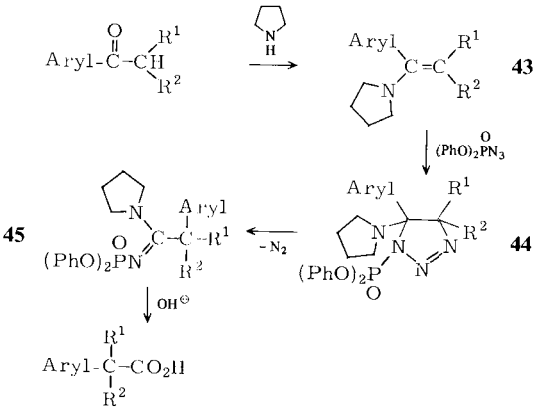
5. Miscellanea

The solvolysis of α-diazoalkyl aryl ketones is not selective and provides rearrangement products **6** in low yield[37].



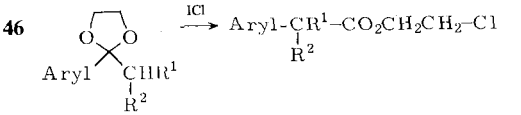
Recently, high selectivity towards the rearrangement has been achieved by masking the carbonyl group as an acetal[18], and an enantioselective synthesis of α-arylalkanoic acid has been accomplished starting from optically active acetals of α-aminoalkyl aryl ketones[38].

Another interesting approach is the three-step process shown in Scheme 5[39]: a) conversion of the ketones with pyrrolidine into enamines **43**, b) 1,3-dipolar cycloaddition of diphenyl azidophosphate to the enamines to give **44**, followed by aryl migration to give **45**, and c) hydrolysis of the resulting *N*-phosphorylated amidines.



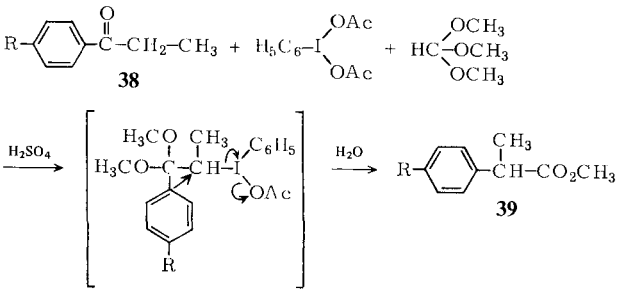
Scheme 5.

Esters of α-arylalkanoic acids have also been obtained by reacting 2-alkyl-2-aryl-1,3-dioxolanes **46** with iodine (I) monochloride in dichloromethane[40], a process which is quite similar to the rearrangement of cyclic acetals of the α-haloalkyl aryl ketones, e.g. **28**.



The oxidative rearrangement of acetylpyrroles is a key step in the synthesis of porphyrins with "natural" acetic acid side-chains. Generally, this rearrangement has been performed using thallium(III) salts. *Franck* et al. have now succeeded in rearranging acetals of suitable α-halogenoalkyl aryl ketones in the presence of silver ions[41].

Oxidation with *m*-chloroperbenzoic acid of the ethylene acetals of α-phenylseleno- or α-phenyltelluroethyl aryl ketones affords hydroxyethyl 2-arylpropanoate in moderate to good yields via aryl group migration[42]. Very recently it was reported that the reaction of ethyl aryl ketones **38** with (diacetoxyiodine)benzene in trimethyl orthoformate in the presence of sulfuric acid leads to methyl 2-arylpropanoates **39** in good yield (Scheme 6)[43].



Scheme 6.

6. Conclusions

Several syntheses of important α-arylalkanoic acids are based on the rearrangement of α-functionalized alkyl aryl ketones. A key point of all these processes is the change of

the hybridization of the carbonyl carbon atom from sp^2 to sp^3, realized by masking it as acetal. Among the various methods available, the most simple appears to be the rearrangement of α-haloalkyl aryl ketones, which has been developed on an industrial scale. The rearrangement can be promoted either by a catalytic amount of metal salts[20], or by protic solvents[22,23]; both methods overcome toxicity problems related to the use of thallium(III) salts[33].

In our opinion, the rearrangement of α-functionalized alkyl aryl acetals to derivatives of α-arylalkanoic acids, thanks to its simplicity, high yields, and clean S_N2 mechanism in the key step, is promising for the direct synthesis of enantiomerically pure compounds.—The present review, constituting a meaningful contribution to the chemistry of "benzenium ions", will hopefully further stimulate synthetic and theoretical studies in the field.

We thank Prof. F. Minisci and Dr. A. Garbesi for helpful discussions.

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Pyrylium Mediated Transformations of Primary Amino Groups into Other Functional Groups**

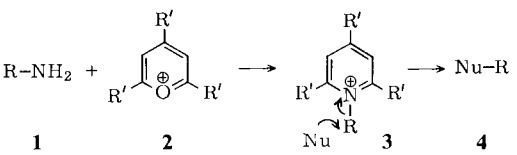
New Synthetic Methods (41)

By Alan R. Katritzky* and Charles M. Marson

The first pyrylium salt was isolated some 80 years ago, yet up to the 1950s only moderate interest was taken in the preparation, properties and uses of such salts. However, the past thirty years has seen a phenomenal growth in the literature pertinent to this area of chemistry: the importance of pyrylium salts as intermediates has been realized. They are readily prepared by a variety of generally applicable routes, and they are highly reactive towards nucleophiles. Together, this enables the convenient synthesis of a great variety of acyclic and heterocyclic compounds. We have used highly substituted pyrylium salts for the two-step conversion of the amino group in alkylamines RNH_2 into numerous other functionalities. In the first step, the pyrylium salts are converted with the amines into *N*-substituted pyridinium salts, which, in the second step, react with $Nu^{\ominus}$ to give the desired products RNu. In some cases the R moiety is also changed, e.g. by elimination. Studies of the reactions of these pyridinium salts have allowed interesting insights into the mechanisms of nucleophilic substitution, in addition to rendering aliphatic amines important synthetic intermediates. Thus, the method complements the diazotization procedure for the transformation of arylamines.

1. Introduction

For the last eight years, first at the University of East Anglia in England and more recently at the University of Florida, our research team has been engaged in investigations aimed at transforming primary amino groups into other functional groups using pyrylium salts as reagents. By 1980, when this work was first reviewed[1], it was already possible to replace primary amino groups in compounds of the type RNH_2 by a large number of functionalities by means of the reaction sequence **1** + **2** → **3** → **4** (Scheme 1).



Scheme 1. Conversion of amines **1** with pyrylium ions **2** via pyridinium ions **3** into the compounds **4** and pyridine derivatives.

Over the past four years, our work has concentrated on the definition of conditions under which both steps of the sequence could be carried out under mild conditions. It has also been concerned with elimination reactions, radicaloid reactions, intramolecular reactions, replacement of NH_2 groups of arylamines by other functionalities, and possible applications to biologically important molecules, particularly in aqueous solution. It is with these aspects that this review covering the period 1980 to 1984 will be principally concerned.

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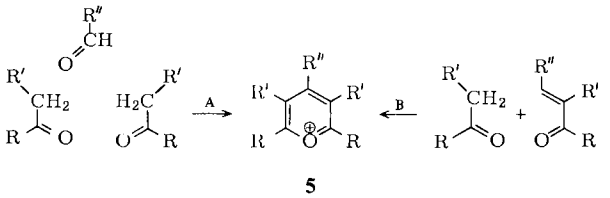
[**] Unless the contents demand otherwise, the qualifiers primary, secondary, and tertiary used in this article refer explicitly to the nature of the alkyl group attached to the amino functionality, and not to the degree of substitution of the latter.

A comprehensive monograph on pyrylium chemistry has appeared in the interim[2].

2. Preparation of Pyrylium Salts

Particularly in connection with our search for good leaving groups for nucleophilic displacements, we have synthesized many dozens of salts containing pyrylium ions **5**. In most cases we have used one of the two routes shown in Scheme 2.

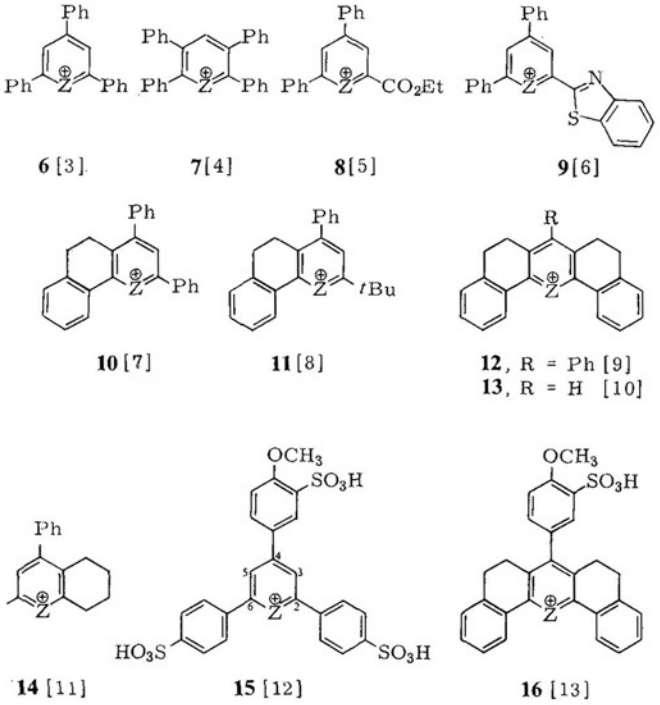


Scheme 2. Preparation of *A*) symmetrical and *B*) symmetrical or unsymmetrical pyrylium ions **5**.

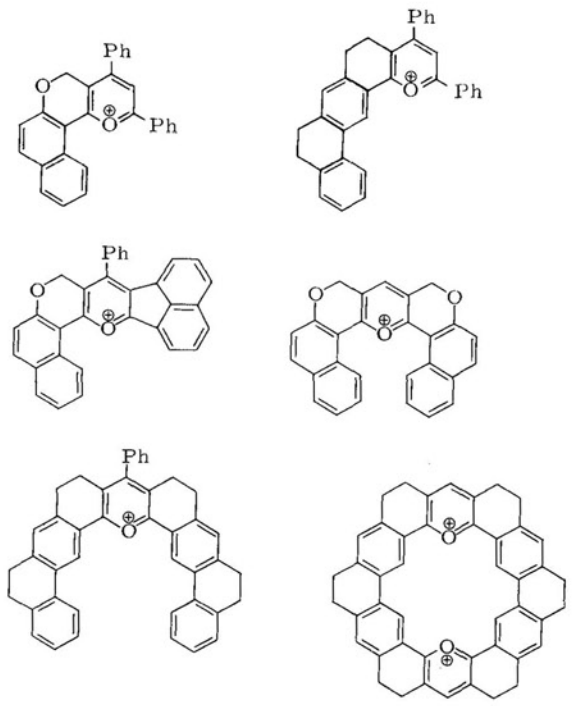
The species **6a**—**16a** shown in Scheme 3 count among the most useful pyrylium salts: their particular uses are mentioned later in this review. Further pyrylium ions that have been investigated are presented in Scheme 4.

3. Conversion of Amines into Pyridinium Salts

^{13}C-NMR spectroscopy has proven very useful for investigating the mechanism of the conversion of amines with pyrylium salts into pyridinium salts. It has been possible to assign all the signals in the ^{13}C-NMR spectra of pyrylium salts, 2*H*- and 4*H*-pyrans, divinylogous amides, diketones, pyridinium salts, pyridines, and anilines[14]. With this information it could be shown that *prim*- and *sec*-alkylamines, RNH_2 and RR'NH, respectively, react with 2,4,6-



Scheme 3. Useful pyrylium ions **6a** – **16a**, Z = O, and corresponding pyridinium ions **6b** – **16b**, Z = NR. References are given to preparative methods of the pyrylium salts.

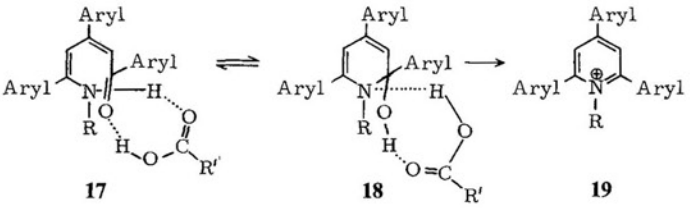


Scheme 4. Polycyclic pyrylium ions.

triarylpyrylium ions by fast ring opening to yield vinylogous amides, which, in the former case slowly cyclize to pyridinium salts[15].

More precise kinetic investigations have been carried out with the aid of ultraviolet spectroscopy. These have shown that the initial reaction with pyrylium ions to give the vinylogous amides is fast under all conditions in the case of strongly basic *prim*-alkylamines, whereas base catalysis is necessary in the case of weakly basic amines[16].

The acid-catalyzed ring-closure of the intermediate divinylogous amides **17** to give the pyridinium derivatives **19** is subject to steric and electronic hindrance. The preferred catalysts are carboxylic acids[17]. Probably the rate-determining, acid-catalyzed step is an electrocyclic ring closure **17** → **18**.



The information gained from these mechanistic and kinetic investigations made it possible to find mild preparative conditions under which amines can be rapidly converted into pyridinium salts at room temperature in only mildly acidic or basic media[18]. The correct preparative conditions have been investigated for reactions of *prim*-alkylamines in which the alkyl group is either primary or secondary as well as (including weakly basic) *prim*-arylamines with a variety of types of pyrylium salts, including those containing bulky α-substituents[19].

4. Nucleophilic Attack on Pyridinium Salts—Mechanisms and Reaction Rates

Extensive mechanistic investigations on the reaction of *N*-substituted pyridinium salts with nucleophiles have shown that the *N*-substituents can be displaced by any of the four routes and five mechanisms depicted in Scheme 5[20]. It is not possible to discuss the mechanistic and kinetic work in detail here in the space available; this will be reviewed elsewhere[21].

The S_N2 rates of reactions of *N*-substituted pyridinium salts with piperidine in chlorobenzene serve as a measure of the reactivity of such salts. Based on a wide range of kinetic results, the following conclusions have been reached:

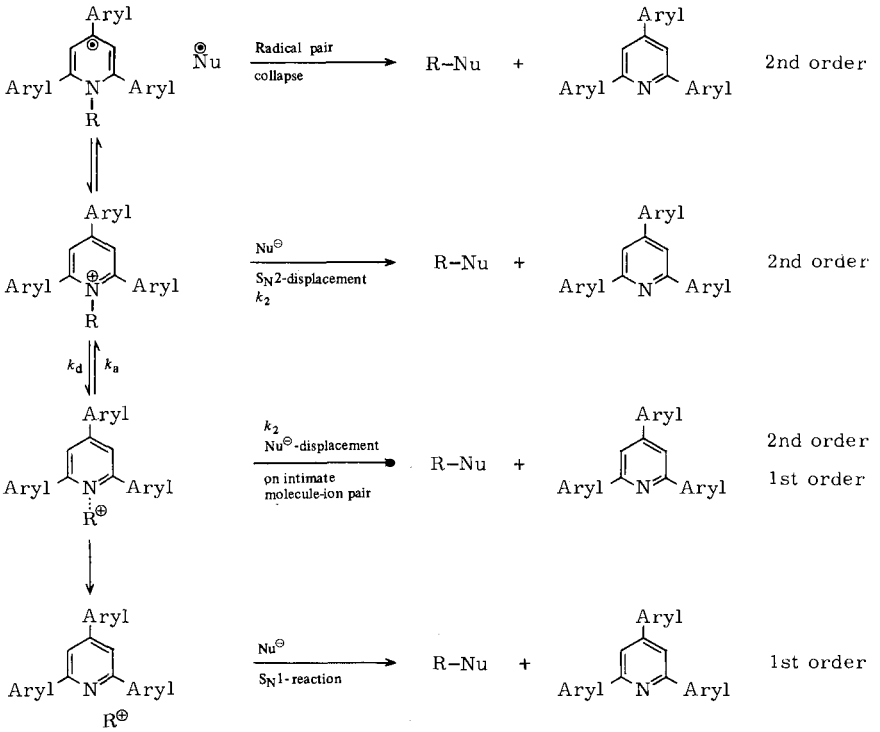
a) In **6b**, *N*-benzyl and *prim*-*N*-alkyl groups are displaced exclusively by S_N2 reactions, whereas *sec*-*N*-alkyl groups undergo displacement by both S_N1 and S_N2 mechanisms.

b) Replacement of α-phenyl groups in **6b** by methyl, *tert*-butyl, or H leads to considerably slower displacement rates.

c) Constrainment of the α-phenyl group to near planarity as in **10b** and **12b** markedly increases the displacement rates. Increased rates are also found for electron-withdrawing substituents, as in **8b** and **9b**.

5. Further Examples of the Transfer of *N*-Alkyl Substituents from Pyridinium Salts to Nucleophiles by S_N2 Reactions

It is now possible to transform primary amino groups into many other types of functionality via intermediate pyridinium ions. Leading references are given in Table 1. Most of the more recent work along these lines has con-



Scheme 5. Alternative mechanistic pathways for the nucleophilic displacement of *N*-substituents from pyridinium ions.

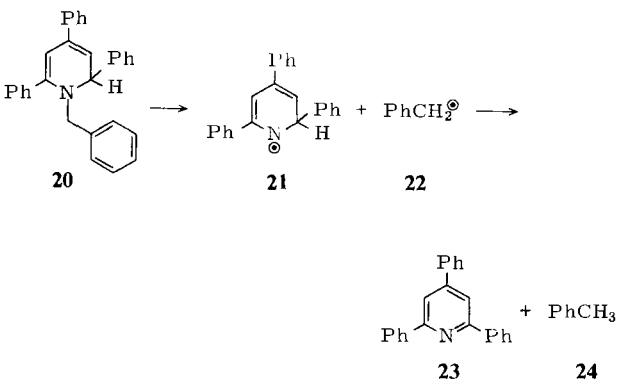
Table 1. Reactions of amines according to the "pyrylium method". The products mentioned in the four vertical columns arise via exchange with nucleophiles from the 4th, 5th, 6th, and 7th main groups of the periodic table.

Replacement of the amino group by hydrogen [28, 29]			
Conversion of amines into			
Malonates [30]	Phthalimides [32]	Carboxylic esters [34]	Fluorides
Nitroalkanes [31]	Sulfonamides [32]	Nitrates [23]	[35, 36]
	Tertiary amines [33]	Ethers [33]	Chlorides
	Ammonium salts [24]		[40, 41]
	Azides [32]		Bromides
			[9, 40]
		Sulfones [22]	Iodides
		Thioethers [33]	[50, 51]
		Dithiocarbonates [37]	
	Phosphonium	Xanthates [7]	
	salts [33]	Thiocyanates [37–39]	
		Selenocyanates [49]	
Elimination to olefins [42–44]			
Elimination/Rearrangement to			
Isocyanates [45, 46]			
Carbodiimides [47, 48]			

centrated on obtaining such conversions under mild conditions in solution. It has been shown that the use of the pentacyclic pyridinium compound **12b** and phase transfer catalysis permits conversion of *prim*-alkylamines RCH_2NH_2 into primary alcohols (sodium (*o*-hydroxymethyl)benzoate is used as nucleophile and phthalide is eliminated), sulfones (from sulfinate ions), thioethers, and ethers at below 100°C in solution[22]. Nitrate ion in refluxing dioxane similarly gives alkyl nitrates[23], while tertiary amines form quaternary compounds[24], and dichromate oxidation yields carbonyl compounds[24]. Under phase transfer conditions, sodium nitrite and the pentacyclic derivatives **12b** give mixtures of nitro compounds and the corresponding alcohols or alkyl nitrites[25].

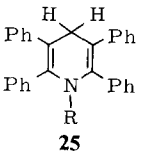
These methods have made it possible to use *N*-neopentyl derivatives of the tricyclic pyridinium compound **10b** and, thus, to prepare neopentyl halides, trifluoroacetate and thiocyanate in good yields without rearrangement[26]. Dialkylamino *prim*-alkylamines are converted by pyrylium salts into the corresponding pyridinium derivatives; these react as aminoalkylating agents with *O*-, *S*-, *N*-, and *C*-nucleophiles and therefore represent safe substitutes for nitrogen mustards[27].

Further work has also been carried out on the replacement of the amino group by hydrogen. Deuterium labeling experiments have demonstrated that the conversion **20** → **23** + **24** proceeds *via* the radical intermediates **21** and **22** (Scheme 6)[29]. The conversion of alkylamines into alkanes can be achieved with the 2,3,5,6-tetraphenylpyridinium ion **7b**[29] or the pentacyclic derivatives **12b** or **13b**[52].



Scheme 6. Thermolysis of 1,2-dihydropyridines **20** to 2,4,6-triphenylpyridine **23** and toluene **24**.

The *N*-alkylated 1,4-dihydropyridines **25** and **26**, which are derived from **7b** and **13b**, thermolyze at approximately 180 and 160 °C, respectively, to give the corresponding alkanes RH. In contrast, however, salts of the pyridinium ion **12b** already give the alkane on heating in solution with diazabicyclononene (DBN)[52]. For the analogous exchange of NH_2 for H in arylamines and heteroarylamines the preferred method is pyrolysis of the tricyclic *N*-aryl and *N*-heteroaryl pyridinium fluorides **10b** $F^{\ominus}$ to give ArH and **27**[53].



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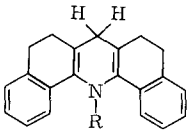

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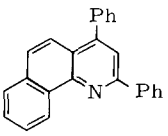
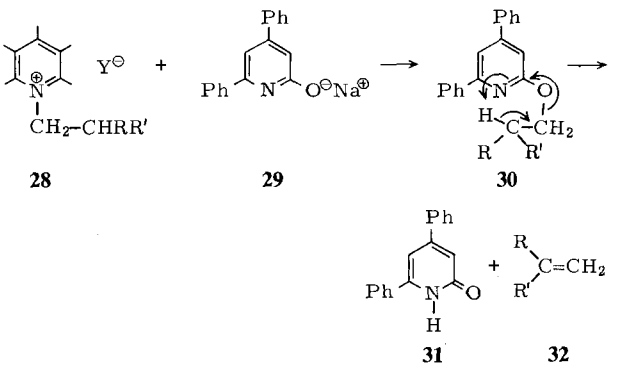


27

6. Formation of Olefins

Since the publication of the previous review[1], conditions for the conversion of primary amines RNH_2 into olefins have been defined. *prim*-Alkylamines are heated with the pentacyclic triflates **12b** at 150 °C in the presence of triphenylpyridine as non-nucleophilic base. In this way olefins can be obtained in yields of 80% or more[42,54]. Nonterminal olefins (20—30%) accompany the terminal olefins. It is believed that the reaction involves an E1 mechanism and that rearrangement of the primary carbonium ion intermediate occurs. *sec*-Alkylamines are converted by the pentacyclic pyrylium ion **12a** directly at 20 °C into olefins via the corresponding secondary carbocations[43]. Thus, cyclohexene (isolated as dibromide in 90% yield) is obtained from cyclohexylamine. These reactions proceed via secondary carbocations and hydrogen shifts are observed. For instance, 3-aminopentane gives some 1-pentene in addition to *cis*- and *trans*-2-pentene.

An alternative method for the preparation of olefins is to heat a pyridinium salt **28** with the sodium salt **29** of 4,6-diphenyl-2-pyridone. The intermediate ether **30** decomposes to pyridone **31** and the olefin **32** (Scheme 7)[55].



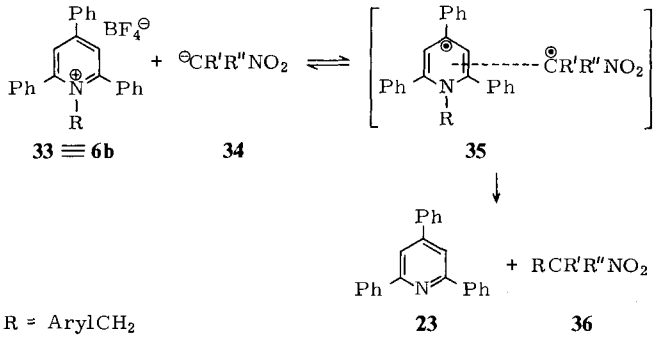
28 **29** **30** **31** **32**

Scheme 7. Synthesis of olefins such as **32** from pyridinium salts **28** using the sodium salt **29** of 4,6-diphenyl-2-pyridone.

7. *C*-Alkylation using Pyridinium Salts: Non-Chain Radicaloid Reactions

The *C*-alkylation of nitroalkane anions such as **34** has been developed into a useful preparative procedure. With the pyridinium ions **33**, unsubstituted and substituted benzyl groups can be transferred to the anions **34** in refluxing ethanol; with nitromethane anions the yields of **36** average 65%. The reaction proceeds much faster in dimethyl sulfoxide as solvent; heating at 100 °C was needed for alkylation, 50 °C sufficed for benzylation. The best yields under these conditions are achieved with 2-nitropropane anions; they are somewhat lower with nitroethane anions, and still lower with nitromethane anions, probably because of further reaction in the last two cases[56]. However, high yields can be achieved if the tricyclic derivative **11b** is used for the transfer of *prim*-alkyl groups and the tricyclic derivative **10b** for the transfer of *sec*-alkyl groups[31].

The following modifications to the 2-phenyl group in 2,4,6-triphenylpyridinium salts do not greatly affect the rate of radicaloid nucleophilic displacement of the *N*-benzyl group by the anion of 2-nitropropane: insertion of a *p*-nitro, *p*-methoxy, or *o*-methyl group, or replacement of phenyl by α- or β-naphthyl[57].



33 ≡ **6b** **34** **35** **23** **36**

R = $ArylCH_2$

Scheme 8. Reaction of pyridinium ions **33** with nitroalkane anions **34** via the radicaloid intermediate **35**.

There is considerable evidence in favor of a non-chain radicaloid reaction (Scheme 8). Aside from other observations, the following arguments favor participation of radicals rather than a S_N1- or S_N2-type mechanism:

a) *Type of products.* In S_N2 reactions, nitroalkane anions generally give *O*- and not *C*-alkylation products[58].

b) *Dependence of the reaction rate on the N-substituent.* In S_N2 reactions, the rate decreases in the order benzyl > methyl > *prim*-alkyl and *sec*-alkyl. In the radicaloid reactions considered here, however, we find that the *sec*-alkyl derivatives react considerably faster than the *prim*-alkyl and methyl analogues.

c) *Influence of p-substituents in the benzyl moiety.* In the alkylations mentioned here, even this is quite different from the pattern found in "normal" S_N2 reactions with piperidine as nucleophile. In reactions of piperidine with *p*-substituted benzyls the rates decrease along the series methoxy > methyl > hydrogen > nitro. In contrast, in the radicaloid reaction the nitro derivative shows the fastest rate, followed by the methoxy compound and methyl, with the unsubstituted derivative showing the slowest rate. This latter sequence is that expected for radical stabilization.

d) *Dependence of reaction rate on the nucleophile.* The rate of formation of an intermediate charge transfer complex is dependent on the structure of the nucleophile.

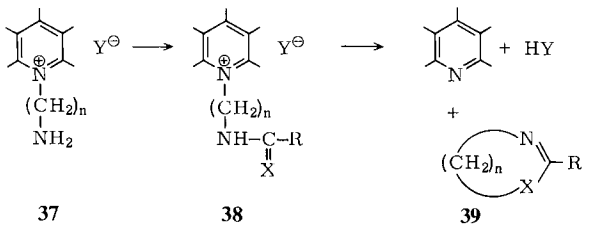
e) *Absolute values of reaction rates and activation parameters.* The absolute reaction rates of the 2-nitropropane anion are much greater than those of piperidine. The activation entropies for the radicaloid reaction are large and negative.

f) *ESR evidence.* ESR spectra show that a charge transfer complex **35** is formed[59].

There is also considerable evidence against a chain-reaction mechanism. First and foremost, clean kinetics are found. It is further significant that initiators and inhibitors do not alter the rates greatly[59][*]. Polarography of pyridinium ions also supports the mechanism described above[61].

8. Intramolecular Reactions with Participation of the *N*-Alkyl Substituents of Pyridinium Salts

The pyridinium ion **12b** derived from 5-aminopentanol was cyclized to tetrahydropyran in 78% yield[62]. Although ethylene oxide was obtained from **6b**, R = 2-hydroxyethyl[63], the pyridinium salts (**6b**, **12b**) derived from other 2-hydroxyamino compounds gave aldehydes or ketones via a 1,2-hydrogen or methyl group migration[62]. The ω-aminoalkylpyridinium salts **37** obtained from diamines can be acylated and converted into ureas or thioureas **38**. On heating in solution, these products cyclize to 4,5-dihydrothiazoles, 5,6-dihydro-4*H*-1,3-thiazines, 4,5-dihydro-1,3-oxazoles, 5,6-dihydro-4*H*-1,3-oxazines, or 4,5,6,7-tetrahydro-1,3-triazepines **39** (Scheme 9)[62].

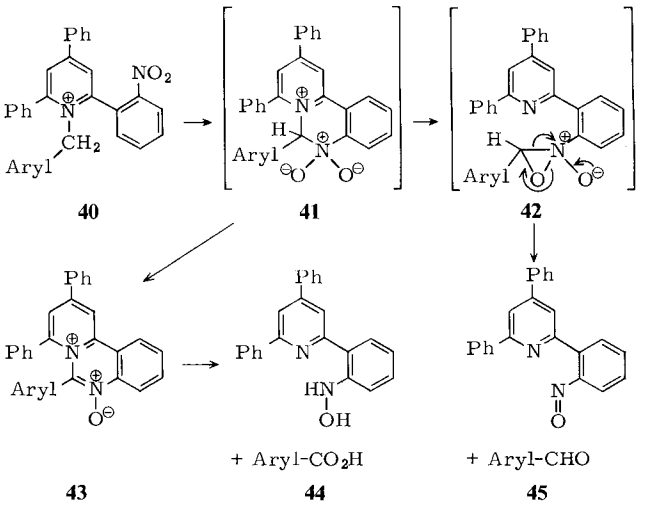


Scheme 9. Intramolecular reactions of *N*-(ω-aminoalkyl)pyridinium salts **37**.

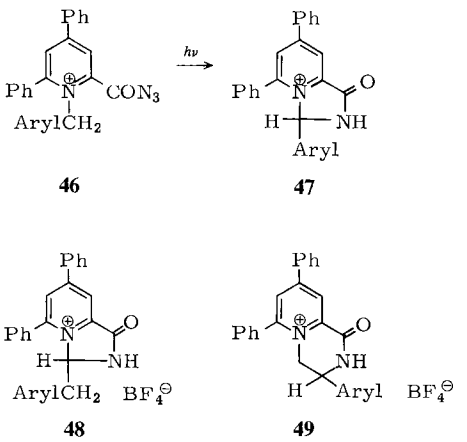
Intramolecular cyclizations between the *N*-substituent and an α-substituent on the pyridine ring are known which proceed via both radical and ionic mechanisms. Pyridinium compounds **40** derived from the 2-(2-nitrophenyl)-4,6-diphenylpyrylium ion and benzylamines undergo intramolecular redox reactions to give mixtures of benzaldehydes (**41** → **42** → **45**) and benzoic acids (**41** → **43** → **44**) according to Scheme 10[64].

On photolysis, the 2-azidocarbonyl-*N*-benzylpyridinium ions **46** are converted via imidazole derivatives **47** into benzaldehydes. Under the same conditions, the *N*-phenethyl derivatives give mixtures of phenylacetaldehydes (via **48**) and benzaldehydes (via **49**)[65].

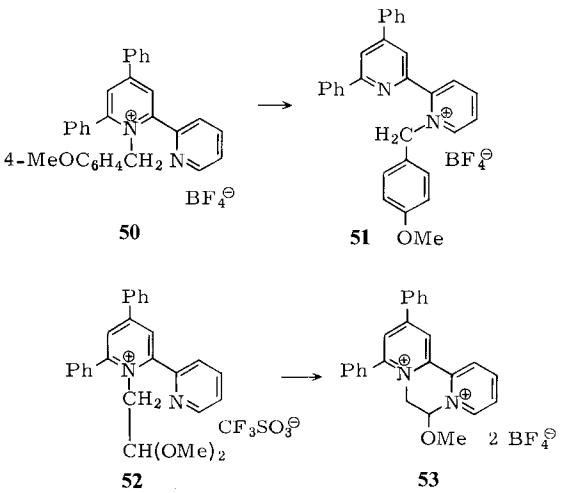
[*] This mechanism was originally referred to in our preliminary communication [30] as the $S_{RN}2$ mechanism. At the time we submitted this communication such a designation had not been previously used. However, in a paper that appeared after submission, but before publication, of our manuscript, *Bunnett* [60] used it in a different way, and we have therefore discontinued its use [59].



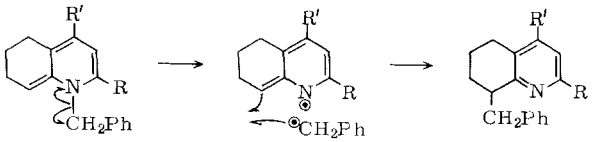
Scheme 10. Conversion of *N*-benzyl-2-(2-nitrophenyl)-4,6-diphenylpyridinium ions **40** into benzaldehydes **45** and benzoic acids **44**.



The transformation **50** → **51** has also been achieved; here a 4-methoxybenzyl group migrates from the pyridinium ring to the nitrogen atom of an α-(2-pyridyl) substituent[66]. This is likely to be an S_N1 process with the benzyl carbocation being trapped by the second nitrogen atom. Concerted intramolecular S_N2 displacement is unlikely, considering the geometric requirements[66]. The cyclization **52** → **53** has also been observed[66].



Considerable work has been carried out on "pyridinium anhydrobases" such as the 2,4-disubstituted 1-benzyl-1,5,6,7-tetrahydroquinolines **54**[67]: On thermolysis of these compounds, *N*-benzyl and *N*-ethyl groups migrate to the neighboring methine carbon atom C-8. Crossover experiments indicate an intermolecular process, probably involving the homolysis shown in Scheme 11[68].

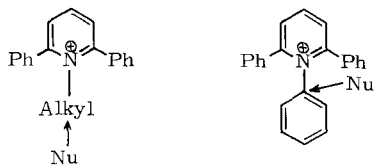


54 **55** **56**

Scheme 11. Rearrangement of "pyridinium anhydrobases" such as **54**.

9. Conversion of the NH_2-Group in Arylamines and Heteroarylamines into Other Functional Groups

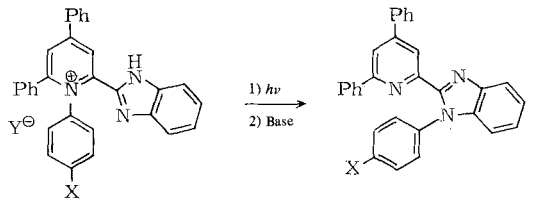
In our previous review we showed that *N*-arylpyridinium salts normally do not undergo nucleophilic displacement reactions[1]. Exceptions are the pyrolysis of the iodides of **6b** (R = aryl) at temperatures above 200 °C[51] and the thermolysis of the thiocyanate of **10b** (R = aryl) above 220 °C[39].



57 **58**

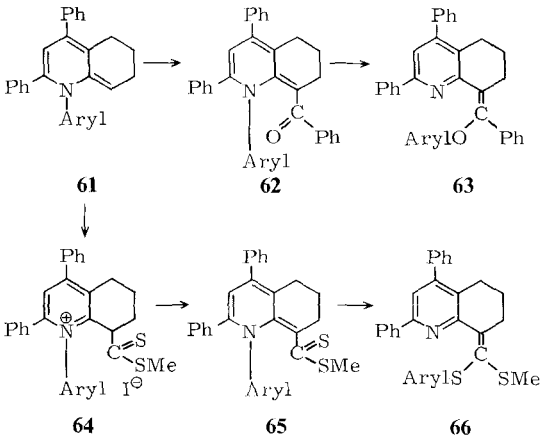
Scheme 12. Difference in steric approach of nucleophiles to *N*-alkyl- and *N*-arylpyridinium ions.

The stereoelectronic requirements for intermolecular nucleophilic displacements of *N*-aryl groups are not favorable, as seen on comparing **58** with **57** (Scheme 12). By way of contrast, however, intramolecular displacement of an *N*-aryl moiety to a suitable α-substituent on the pyridine ring should be possible. The first example of this kind of displacement was found in the photochemical rearrangement **59** → **60**[69].



59 **60**

More recently, it has been possible to demonstrate a series of non-photochemical rearrangements of this type. Such reactions are related to the well-known Smiles rearrangement[70], but our reactions occur under milder conditions and, in particular, do not require activating substituents in the displaced aryl ring.

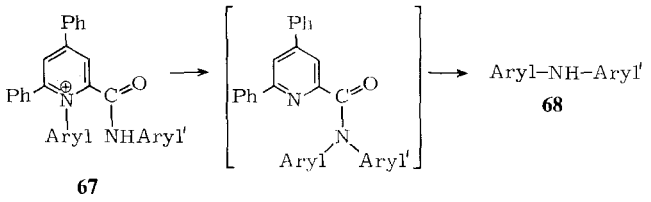


61 **62** **63** **64** **65** **66**

Scheme 13. Rearrangement of *N*-aryldihydropyridines such as **62** and **65**.

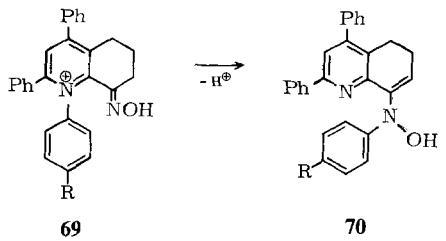
Thus, anhydrobases **62** (obtained from **14b** via **61**) rearrange at 150 °C into the isomeric aryl enol ethers **63**, which can be readily hydrolyzed to the corresponding phenols[71]. Alternatively, the compounds **61** can be converted by carbon disulfide and methyl iodide into the thio derivatives **64**, which afford the new anhydrobases **65**. These rearrange thermally into ketene-*S*,*S*-dithioacetals **66** (Scheme 13)[72].

Reaction of 2-ethoxycarbonyl-4,6-diphenylpyrylium ions **8a** with ring-substituted anilines leads, via the pyridinium ions **8b**, to the carboxamides **67**, which react with



67 **68**

sodium hydride in refluxing toluene to give diarylamines **68** in overall yields of ca. 30%; this compares favorably with other methods for the synthesis of diarylamines lacking active substituents[73]. The second amine used to form the amide can also be *tert*-butylamine or neopentylamine[74].

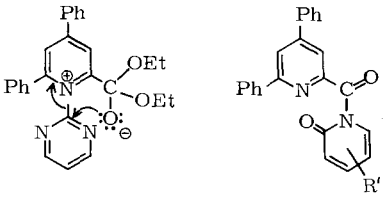


69 **70**

Another reaction in which a fragment of a molecule is transferred to nitrogen is the conversion of *N*-aryl-8-hydroxyimino-5,6,7,8-tetrahydroquinolinium ions **69** into **70**[74]. Attempts to transfer *N*-aryl groups to carbon atoms are still in progress[75].

An intermolecular nucleophilic displacement of the 2-pyridyl group in 2,4,6-triphenyl-, 2,4-diphenyl-, or 4-phenyl-*N*-(2-pyridyl)pyridinium salts under mild conditions has so far not been achieved[76]. However, it was found that

the 2-ethoxycarbonyl-4,6-diphenyl-*N*-(2-pyrimidinyl)pyridinium ion **8b** smoothly rearranges in the presence of ethanolic sodium ethoxide to give the corresponding 2(1*H*)-pyrimidinone via intramolecular attack, as shown in formula **71**[76].



71 **72**

Following this work it was shown that the cations **8b**, which are readily accessible from substituted 2-aminopyridine, are converted by dilute sodium hydroxide at 25°C into the corresponding *N*-pyridylcarbonyl-2-pyridones **72**, which, in turn, readily hydrolyze to 2-pyridones[77].

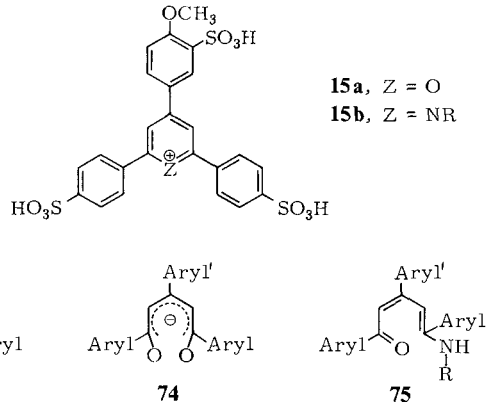
10. Biological Applications: Reactions in Aqueous Solution

Pyrylium salts show several potential advantages for the modification of the primary amino groups of complex natural products in the presence of other functional groups.

Thus, pyrylium ions react specifically with amines of the type RCH_2NH_2; on the other hand, no irreversible reaction occurs with compounds of the type RCO_2H, ROH, RCHO, RSH, R_2NH, RCONHR′, $RCONH_2$, RSR′, etc. Amino groups bound to *prim*-alkyl residues react at very different rates with the same pyrylium derivative, depending on the chemical environment. The method is therefore suitable for semi-synthetic transformations of natural products provided the reaction $RNH_2 \rightarrow$ pyridinium salt in presence of H_2O is possible, and provided the pyridinium moiety can be displaced by other substituents under mild conditions.

Preliminary attempts to react amino acids with triphenylpyrylium salts were unsuccessful owing either to the inactivation of the pyrylium salts by rapid formation in water of insoluble enedione pseudobases, or to the insolubility of amino acids in the common organic solvents (e.g. dichloromethane or absolute ethanol) normally used for the preparation of pyridinium salts. Although primary amines react with triphenylpyrylium ions in solvents of high polarity (e.g. triethylamine/carboxylic acid mixtures or phenols) to give the usual pyridinium salts, α-amino acids suffer spontaneous decarboxylation under these conditions, yielding *N*-alkylpyridinium salts. However, formation of pyridinium salts without further decomposition occurs with the ω-amino and terminal amino groups of lysine and glycylglycine, respectively, which serve as models for amino residues in polypeptides and proteins[78].

Alkyl esters of α-amino acids likewise react with pyrylium salts; however, the *N*-(α-ethoxycarbonylalkyl)-2,4,6-triphenylpyridinium salts thus formed are very unreactive towards nucleophilic substitution[79]. This is ascribed to stereoelectronic effects: the normal activating influence of an α-carbonyl group on the displacement of say a bromine atom is due to the possibility of overlap between the incoming nucleophile and the anti-bonding orbital of the carbonyl group. Models indicate that this is impossible in the pyridinium derivatives just mentioned[79].



15a, Z = O
15b, Z = NR

73 **74** **75**

For these reasons, it was decided to prepare water-soluble pyrylium salts. Tris(sulfophenyl)pyrylium ions such as **15a** co-exist in aqueous solution with the soluble enedione pseudobase **73**, and the anion **74**. The kinetics and equilibria of these species and the corresponding 2*H*-pyran and hydroxydienone have been elucidated over a wide pH range[12]. The pyrylium ion **15a** reacts with amines in aqueous solution to give mixtures of divinylogous carboxamide **75** and pseudobase **73**. The two products are formed by kinetic control in quantities which then equilibrate. **75** cyclizes to pyridinium ions **15b**; more pyridinium ion is then slowly formed from the pseudobase **73**. Rate constants were measured for reactions with lysine and other typical primary amines[80].

Other water-soluble triarylpyrylium salts and zwitterions containing two or three carboxylic or sulfonic acid groups and 2,6-diaryl-4-carboxypyridinium derivatives have been prepared[81,82].

In order to determine the best conditions for maximizing the yields of pyridinium salts from pyrylium salts and amines, the equilibria and kinetics of representative water-soluble pyrylium salts have been measured in aqueous solution, and the competing reactions with amines, water molecules and hydroxide ions elucidated and rationalized[83].

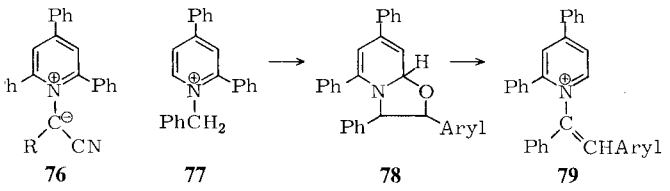
The reactions of gelatin and chymotrypsin with 4-(4-methoxy-3-sulphophenyl)-2,6-bis-(4-sulphophenyl)pyrylium ions **15a** in aqueous buffer have been investigated. The first-order ring-closure of the divinylogous carboxamide groups thus formed proceeds at a rate comparable with that of the reaction of **15a** with free lysine[84].

Kanamycins A and B react exclusively at the 6-amino groups with a variety of water-soluble pyrylium ions in aqueous solution to give the corresponding pyridinium ions in high yields. Neomycin reacts at the 1-amino group[85].

The ω-amino group of lysine has been replaced by PhS and $PhCH_2S$ groups via intermediates of the type **16b** in two-step reactions in aqueous solution, and at temperatures not exceeding 75°C. The terminal amino group of glycylglycine can be replaced in an analogous way by a PhS function[13]. These reactions provide models for the selective conversion of the ω-amino group of lysine side chains and the terminal groups of glycine residues, respectively.

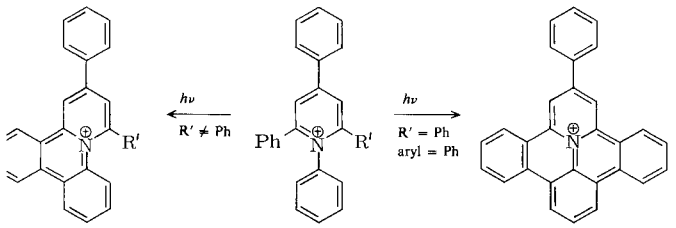
11. Other Reactions of the *N*-Substituents of Pyridinium Salts

Pyridiniomethanides have been utilized in various syntheses by *Kröhnke*[86]. We have also investigated such ylides. When another electron-withdrawing group is situated on the carbon atom, the ylide becomes quite stable, as, e.g., the compounds **76** derived from *N*-(cyanomethyl)pyridinium salts[87]. *N*-Benzyl-2,4-diphenylpyridinium ions **77** react with benzaldehydes to give the oxazolopyridines **78**, which can be dehydrated to the *N*-(β-styryl) derivatives **79**[5]. (4,6-Diphenyl-2-pyridinio)formates react with *p*-nitroso-*N*,*N*-dimethylaniline to give nitrones in an extension of the Kröhnke reaction[88].



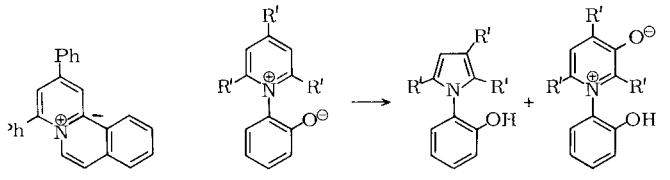
76 **77** **78** **79**

Pyridiniomethanides also add to carbonyl groups in aldol-type reactions, and to active CC double bonds in Michael reactions[89]. 1,2,4-Triarylpyridinium ions **81**, R ≠ Ph, undergo photocyclization and 1,2,4,6-tetraarylpyridinium



80 **81** **82**

cations **81**, R′ = Ph, photobiscyclization to form condensed ring systems **80** and **82**, respectively[90,91]. These compounds form pseudobases very readily[92]. Somewhat similar ring-systems (e.g., **83**) have been obtained by cyclization of pyridinium salts derived from 2,2-dimethoxyethylamine[93].

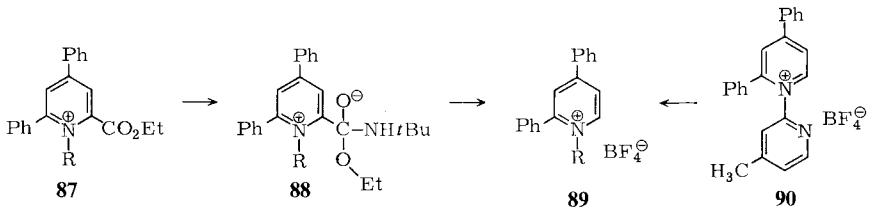


83 **84** **85** **86**

2-(2,4,6-Triaryl-1-pyridinio)phenolates **84** (and the corresponding 1-substituted 2-naphtholates) are oxidized by H_2O_2: mixtures of tetraarylpyrroles **85** and 3-pyrimidiniooxides **86** are formed. 2,4,6-Triaryl-*N*-phenylpyridinium salts react with H_2O_2 to give β-(arylcarbonylamino)chalcones[94]. *N*-(α-Methylallyl)pyridinium salts rearrange to the *N*-(γ-methylallyl)-analogues.

12. Preparation of Pyridinium Salts without α-Substituents

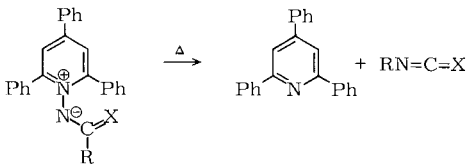
Some of the work described in this review has required the availability of pyridinium derivatives with unsubstituted α-positions. Such compounds cannot be prepared directly from pyrylium precursors, since ring-closure to the pyridinium derivative does not occur very readily in this case. However, we have found that α-ethoxycarbonyl substituents in pyridinium salts are removed completely by refluxing with *tert*-butylamine (e.g., **87** → **88** → **89**). With other amines, $S_NANRORC$ reactions compete[95]. This method has been utilized for the preparation of 1,4-diarylpyridinium salts[96]. An alternative method involves utilization of *N*-(4-methyl-2-pyridyl)-2,4-diphenylpyridinium tetrafluoroborate **90**, which reacts with a variety of amines to give the corresponding *N*-substituted 2,4-diphenylpyridinium salts **89** directly[97].



87 **88** **89** **90**

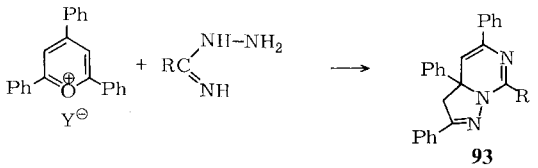
13. *N*-Amino-Substituted Pyridinium Salts

Scheme 14 shows the previously described conversion of *N*-(1-pyridinio)carboxamidates **91** into isocyanates[46] and of *N*-(1-pyridinio)carboxamidinates into carbodiimides[48] (for further details see [1]). More recently we have found that the compounds **92** are conveniently accessible from *N*-aminopyridinium salts and imidoyl chlorides[98]. However, *N*-unsubstituted amidrazones react with 2,4,6-triphenylpyrylium salts to give, via ring-opening and cyclization, the corresponding pyridines, namely the dihydropyrazolo[1,5-*c*]pyrimidines **93**[98].



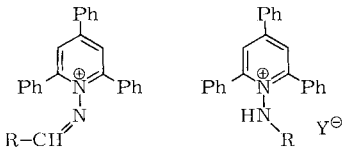
91, X = O
92, X = NR

Scheme 14. Preparation of isocyanates (X = O) and carbodiimides (X = NR) from the pyridiniocarboxamidates **91** and pyridinioamidinates **92**.

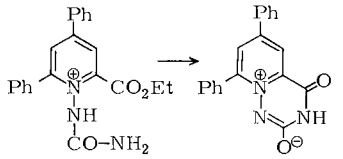


93

N-Amino-2,4,6-triphenylpyridinium tetrafluoroborate reacts with aldehydes to give **94** and with active halides[99] and other electrophiles to give **95**[100].



94 **95**



96 **97**

The copious and widely scattered pertinent literature on the reactions of pyrylium salts with hydrazines has been reviewed. Not only are the reactions of alkyl, dialkyl, and arylhydrazines dealt with but also the chemistry of the acid hydrazides and other electron-withdrawing, substituted hydrazines, and hydrazones[101]. In suitable cases, these reactions, in which a large variety of *N*-aminopyridinium derivatives is formed, are also followed by a cyclization, e.g. **96** → **97**[101].

14. Physical Measurements

Solution and gas-phase basicities of pyridinium salts with bulky α-substituents have been compared with their nucleofugacity[102, 103]. Restricted rotation occurs in polysubstituted pyrylium ions[104]. The gas-phase behavior of these pyridinium ions is currently being investigated by mass spectroscopy[105].

15. Summary and Outlook

In the preceding sections, the particular suitability of pyrylium salts for transforming amino groups into other functionalities has been described. It would now seem appropriate to summarize the disadvantages as well as the advantages of the method. Because of the high molecular weights of the pyrylium reagents, the method is unlikely to be much used for the transformation of simple amines which can be conveniently carried out with analogous halides R-Hal or alkyl tosylates R-Tos. The method will most likely be resorted to,

a) when transformations cannot be carried out at all, or less conveniently, with the corresponding halides or tosylates. Examples here include the *C*-alkylation of nitroalkane anions, the preparation of alkyl and benzyl fluorides, and the conversion of amines into olefins,
b) when the amino compounds are more easily accessible (e.g. from natural sources) than the corresponding halides or alcohols,
c) when amino groups are to be converted selectively. Pyrylium salts do not react with most other functional groups of common natural products. With the new water-soluble pyrylium salts, specific transformation of protein NH_2-groups becomes feasible under mild conditions in aqueous solution. Future work in this area could have important consequences for biological chemistry,
d) when the diazotization of arylamines, despite the usefulness of this method for many transformations, cannot be resorted to without difficulty. Thus, attachment of C-linked functionalities other than CN by diazotization is difficult. In the case of many heteroarylamines diazotization of the normal type is not easily achieved. An example of a possible application of the new alternative method is the mild conversion of nucleic acid NH_2-groups into oxo-groups (via tautomerizing hydroxy groups); the selectivity could be considerably greater than that in the diazotization with nitrous acid.

The kinetic studies outlined in this review made it possible to determine the optimum conditions for amino-group transformations. Moreover, they have shed new light on the mechanism of such transformations. Studies on the solvolysis of pyridinium ions are of importance for the formulation of general theories of nucleophilic substitution in both aliphatic and aromatic systems.

The reactions proceeding via radicaloid intermediates, exemplified here by nitroalkane anions **34**, are being studied in more detail. In particular, we are interested in the conditions which favor the formation of σ-adducts over charge-transfer complexes, and in the possible extension of this reaction to C_{aryl}–C bond formation.

The present work has emphasized the potential importance both of steric acceleration and of the possibility of fast intramolecular reactions of normally unreactive substrates. The field offers considerable potential for molecular design: the pyrylium cation can be considered as a template into which the amine is introduced, and on which any desired functionality can be arranged to facilitate intramolecular transformations of types which are reminiscent of those which apply in enzymes.

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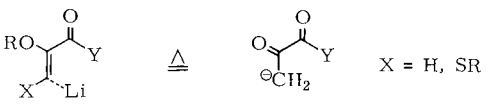
Synthesis of 3-Deoxy-D-*manno*-2-octulosonic Acid (KDO)**

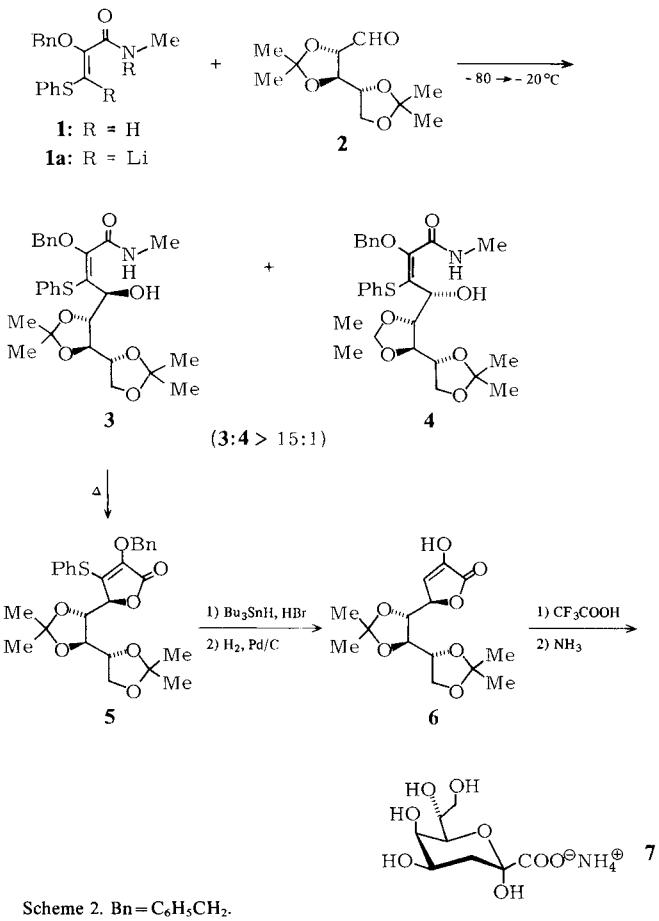
By *Richard R. Schmidt** and *Rainer Betz*

KDO (ammonium salt: **7**) is an integral component of the lipopolysaccharides of gram-negative bacteria[1]. In all the published syntheses, the construction of the D-*manno* structure from D-mannose derivatives with chain lengthening by Wittig reaction required additional steps for the incorporation or liberation of the 2-keto group[1–3]. In the case of its construction from D-arabinose and derivatives, the formation of diastereoisomers and their separation prove to be disadvantageous[4]. The special interest in the chemistry of KDO[1] was the reason for developing, in analogy to the biosynthesis[1], a productive synthesis on the basis of *C*-lithiated, functionally substituted acrylic acid as pyruvic acid-equivalent C_3-building block and D-arabinose as C_5-building block (Scheme 1).



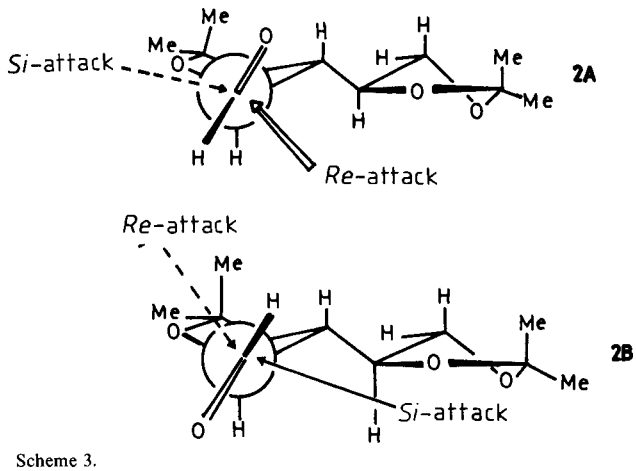
Scheme 1.

A suitable C_3-synthetic building block was found to be 2-benzyloxy-3-(phenylthio)acrylic acid *N*-methylamide **1**[5], which reacts with lithium diisopropylamide in the molar ratio 1:2 directly and almost quantitatively to give the dilithiated species **1a** (Scheme 2). Reaction of **1a** with the readily accessible 2,3:4,5-di-*O*-isopropylidene-D-arabinose **2**[6] as electrophile furnished, in very good yields and with high diastereoselectivity, the desired D-*manno* product **3** (in tetrahydrofuran (THF)/hexamethylphosphoric triamide: 85%, **3**:**4** > 15:1; in THF: 75%, **3**:**4** = 8:1), which recrystallized from the mother liquor in isomerically pure form (m.p. 113–114°C, 75%). Hence, the problem of separating diastereoisomers was solved in an easy way. The diastereofacial selectivity can be explained in terms of the Felkin model[7]. Steric and stereoelectronic influences favor *Re*-attack in the case of **2A**, to give the D-*manno* product, rather than *Si*-attack to give the D-*gluco* product **4** (Scheme 3). In the case of **2B** *Re*- and, in particular, *Si*-attack are handicapped owing to the spatial requirement of the 4,5-*O*-isopropylidene group.



Scheme 2. Bn = $C_6H_5CH_2$.

On heating in petroleum ether (b.p. 110–140°C), **3** was converted almost quantitatively into butenolide **5**[8], which was obtained as a colorless oil after filtration over silica. Cleavage of the phenylthio-group was accomplished by reaction with tributyltin hydride and hydrogen bromide (73% after filtration over silica)[9]. The benzyl group was removed hydrogenolytically with palladium on active charcoal in ethyl acetate; the known KDO intermediate **6** was thus formed as colorless crystals [95%; m.p. 100–104°C, ref. [2] 102–104°C; $[\alpha]_{589}^{25}$ 57.2 ($CHCl_3$, $c = 1$); ref. [2] $[\alpha]_D^{22}$ 56.7 ($CHCl_3$)]. According to ^{1}H-NMR data (250 MHz,



Scheme 3.

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[**] Vinyl Carbanions, Part 19. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.—Part 18: R. R. Schmidt, *Bull. Soc. Chim. Belg. 92* (1983) 825.

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$CDCl_3/C_6D_6 = 4:1$), 10% of **6** is present in the tautomeric keto form.

The methods already described in the literature proved to be satisfactory for carrying out cleavage of the isopropylidene group with aqueous trifluoroacetic acid (85%) and for the isolation of the ammonium salt of **7** from KDO (75%)[2].

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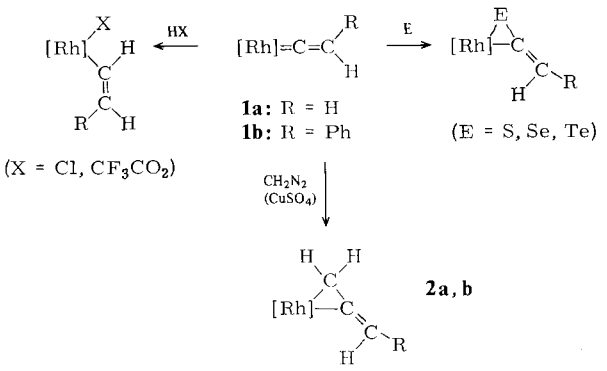
Ambidentate Behavior of Mononuclear Vinylidenerhodium Complexes—Novel C–C Coupling of a Methyl to a Vinylidene Group

By *Helmut Werner*, Justin Wolf, Gerhard Müller,* and *Carl Krüger*

Dedicated to Professor Jan Thesing on the occasion of his 60th birthday

Besides carbenemetal complexes $L_nM{=}CRR'$, the related vinylidenemetal complexes $L_nM{=}C{=}CRR'$ have also attracted increasing interest in recent years[1]. As confirmed by X-ray structure analyses[1], they contain a cumulated π-electron system and may therefore be regarded as "metallaallenes". In the complexes with $L_nM = C_5H_5(iPr_3P)Rh$ and $CRR' = CH_2$, CHMe, CHPh recently prepared by us[2a,b], the M=C and not the C=C bond is the preferred site of attack for electrophiles, as can be seen from the examples given in Scheme 1[2c].

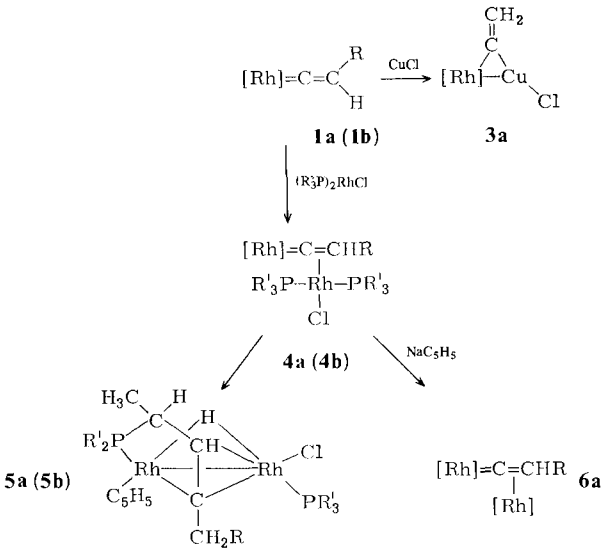
We have now discovered that on using CuCl instead of $CuSO_4$ for the transfer of CH_2 from diazomethane to **1a**, yet another η^5-C_5H_5Rh-containing compound of the composition **3a** is formed in addition to **2a**; it is obtained directly from **1a** and CuCl in tetrahydrofuran (THF) at room temperature in 71% yield[3]. The new complex contains a μ-$C{=}CH_2$ bridge between two different metal atoms, only



Scheme 1. $[Rh] = C_5H_5(iPr_3P)Rh$.

one example of which has so far been reported in the literature[4].

Attempts to prepare a $(\mu\text{-}C{=}CH_2)Rh_2$ complex with a 16-electron fragment $C_5H_5(L)Rh$ on each side of the vinylidene bridge by reaction of **1a** with $C_5H_5Rh(L)CO$ ($L = CO$, PMe_3) or $C_5H_5Rh(PMe_3)C_2H_4$ failed, owing to the poor reactivity of the starting compounds $C_5H_5Rh(L)L'$. However, **1a** reacts rapidly with the 14-electron species $(iPr_3P)_2RhCl$ (pentane, 25°C, 10 min; yield 56%) to give the binuclear complex **4a**[3], in which the "metallaallene" is bound to the square-planar coordinated rhodium atom, similarly to an alkene[5] or an alkyne[2a,b].



Scheme 2. $[Rh] = C_5H_5(R'_3P)Rh$, $R' = iPr$ (P atom of the $C_5H_5(R'_3P)Rh$ group designated as P^1 in the ^{31}P-NMR spectrum of **4a** [3]); **a**: R = H; **b**: R = Ph.

Solid **4a** is stable under inert gases. In solution, elimination of phosphane occurred (at 25°C after several days, at 50°C after 2–3 h), and a binuclear complex containing a hydrido bridge was formed which could not be isolated in analytically pure form; however, both the NMR data as well as the mass spectrum [M^+ at m/z 652 (^{35}Cl), 654 (^{37}Cl)] support formulation of the complex as **5a** (Scheme 2).

Reaction of **1b** with $(iPr_3P)_2RhCl$ (benzene, 25°C, 30 min) leads rapidly (via the ^1H-NMR spectroscopically detectable intermediate **4b**) to the corresponding phenyl derivative **5b** (yield 63%)[3]. The elimination of iPr_3P from **4b** is apparently promoted by the phenyl substituents on the β-C atom of the vinylidene ligand.

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The result of the X-ray structure analysis of **5b** is shown in Figure 1[6]. Double H-transfer from a CH_3 group of a triisopropylphosphane ligand to the Rh_2-moiety and the CHR carbon atom leads to formation of a CH group which is linked to the α-C atom of the original vinylidene ligand and the Rh atom of the starting compound $(iPr_3P)_2RhCl$. The Rh1,P1,C3,C2 fragment of the resulting C_3PRh five-membered ring is planar; the bridging atom Cl is at a distance of 0.39 Å from this plane. The C1–C2 bond length of 1.417(4) Å suggests partial double-bond character, i.e. the bonds drawn between the CC unit and Rh in Scheme 2 are to be regarded as representing a resonance formula. The Rh–Rh bond length of 2.7602(3) Å can be interpreted in terms of a weak Rh–Rh interaction[7]. The Rh1–C1 and Rh2–C1 distances are very similar to those in other, comparable Rh_2 complexes[8]; the Rh2–C2 distance, however, is slightly longer (Fig. 1). Even the values for the Rh–H–Rh bridge differ very little from those of other singly H-bridged systems[9].

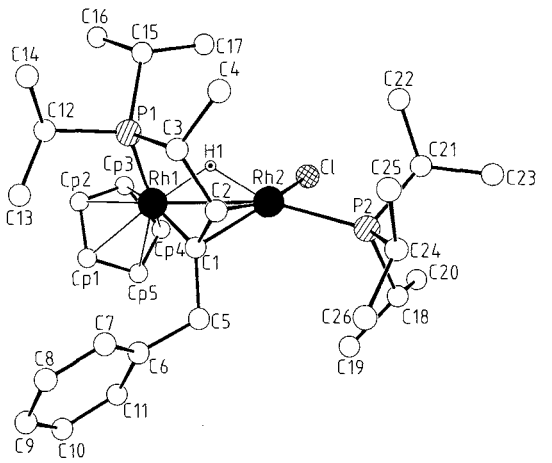

Fig. 1. Structure of the complex **5b** in the crystal. Selected bond lengths [Å] and angles [°]: Rh1–Rh2 2.7602(3), Rh1–H1 1.61(3), Rh2–H1 1.72(3), Rh1–C1 2.053(3), Rh2–C1 2.021(3), C1–C2 1.417(4), C2–C3 1.526(4), C3–C4 1.527(4), C1–C5 1.526(4), Rh2–C2 2.140(3), Rh1–P1 2.230(1), Rh2–P2 2.308(1), Rh2–Cl 2.392(1); Rh1–H1–Rh2 112(2), Rh1–C1–Rh2 85.3(1), Rh1–C1–C2 116.4(2), Rh2–C1–C2 74.7(2).

Reaction of **4a** with NaC_5H_5 (THF, 25 °C, 20 min) leads quantitatively to the binuclear compound **6a**[3], in which the two $C_5H_5(iPr_3P)Rh$ moieties are unequally coordinated to the $C{=}CH_2$-group. Proof of the structure follows from the ^{1}H-NMR spectrum, but principally from the ^{13}C-NMR spectrum (in C_6D_6), in which in addition to the signals for the phosphane and the cyclopentadienyl carbon atoms a signal is found at $\delta = 310.37$ (ddd, $J_{Rh^1C} = 70.6$, $J_{Rh^2C} = J_{PC} = 23.0$ Hz), i.e. in the region typical for carbene and α-vinylidene carbon atoms[1,2a,b]. Attempts to rearrange **6a** into the symmetrical isomer $[C_5H_5(iPr_3P)Rh]_2(\mu\text{-}C{=}CH_2)$ have so far been unsuccessful.

With the synthesis of **4a**, **b** and **6a**, it is shown for the first time that not only the M=C- but also the C=C-bond of a vinylidene complex can react with a coordinatively unsaturated metal species. Thus, complexes of the type $L_nM{=}C{=}CRR'$ behave in an ambidentate way, as demonstrated by the formation of the structurally different binuclear compounds **3a** and **4a** from **1a**.

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Ring-Opening of Methylene-Bridged Dimetal Complexes by Bases**

By *Wilhelm Keim**, *Michael Röper*, *Heinz Strutz*, and *Carl Krüger*

Dimetallacyclopropane complexes are of special interest for the mechanistic explanation of the Fischer-Tropsch synthesis[1]. Ring-opening to well-defined derivatives has hitherto only been accomplished by reaction with strong acids[2]. We have now found that ring-opening of the three-membered ring moiety can also be induced by bases when such complexes contain CO ligands. Reaction of $[Fe_2(\mu\text{-}CH_2)(CO)_8]$ **1**[3] with sodium methoxide leads to the unstable polynuclear methyl metallaacetate complex **2**,

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so far characterized only by IR spectroscopy[4]. Cation exchange with $(Ph_3P)_2N^{\oplus}Cl^{\ominus}$ (PPNCl) afforded the more stable compound **2a**, which, however, could not be isolated in analytically pure form[5]. However, on warming **2a** (in DMSO, 80 °C) the pure, isolable mononuclear product **3** is formed[6].

$$\underset{\mathbf{1}}{Fe_2(\mu\text{-}CH_2)(CO)_8} + NaOCH_3 \xrightarrow{THF} \underset{\mathbf{2}}{Na^{\oplus}[Fe_n(CO)_m(CH_2COOCH_3)]^{\ominus}}$$

$$\xrightarrow[2.\ 80\ °C/18\ h]{1.\ PPN^{\oplus}Cl^{\ominus}} \underset{\mathbf{3}}{PPN^{\oplus}[(CO)_4Fe(CH_2COOCH_3)]^{\ominus}}$$

The geometric data of the central moiety in the anion of **3** (Fig. 1) correspond to those of tetracarbonyl(propyl)ferrate[7].

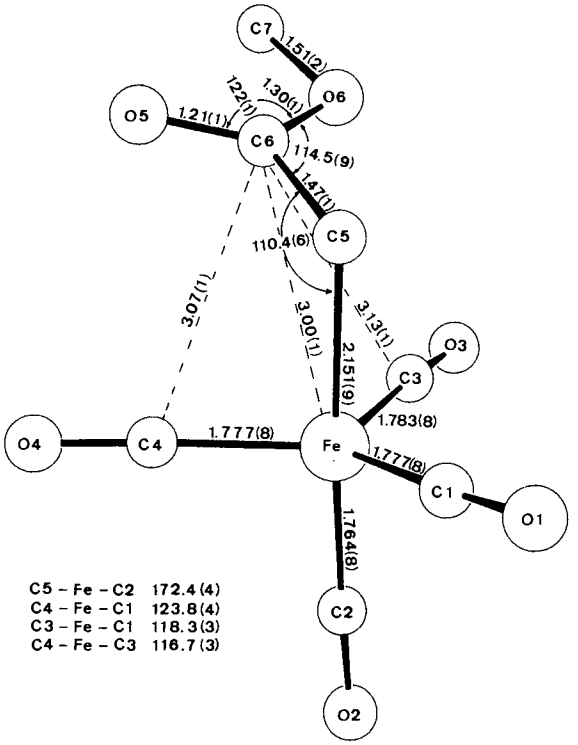
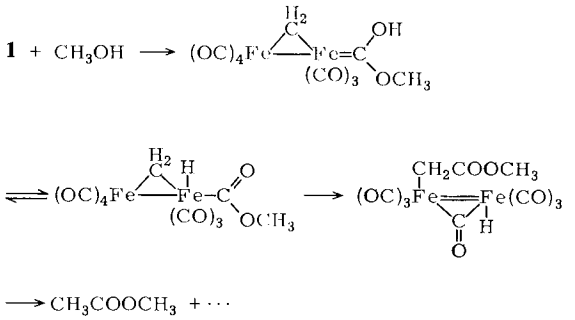


Fig. 1. Structure of the anion of **3** in the crystal, with important atomic distances [Å] and angles [°]. Space group $P2_1/n$ (No. 14). $a = 24.798(5)$, $b = 9.483(2)$, $c = 35.606(4)$ Å, $\beta = 108.23(1)°$, $V = 7952.51$ Å^3, $\rho_{calc} = 1.302$ g cm^{-3}, $Z = 8$ (4 × 2 molecules); $\lambda = 0.71069$ Å, $\mu(Mo_{K\alpha}) = 5.02$ cm^{-1}, 13891 reflections, 5923 observed ($I > 2\sigma(I)$), refined parameters 913, $R = 0.0599$, $R_w = 0.0739$. Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD 50744, the names of the authors, and the journal citation.

The intermediate product **2** is formed by nucleophilic attack of the methoxide base at a CO ligand of **1**, and its subsequent coupling with the CH_2-bridge ligand. Such a reaction sequence is also supported by the detection of $Li^{\oplus}[Fe_2(\mu\text{-}CH_2)(CO)_7(COR)]^{\ominus}$ **4** (R = Me, *n*-Bu) as product of the reaction of **1** with methyl- or butyllithium[8a]. Reaction of **4** with trifluoroacetic acid in tetrahydrofuran leads to acetaldehyde and acetone (yield 3.4 and 3.6% referred to **1**, R = Me) or to valeraldehyde and 2-hexanone (yield 4.8 and 2.1%, respectively, referred to **1**, R = *n*Bu).

The formation of **3** from **1** corresponds to a homologation of the methylene function within the coordination sphere of a complex. The cobalt complex $[Co_2(\mu\text{-}CH_2)Cp_2(CO)_2]$[9] reacts analogously, whereas the iron complex $[(Fe_2(\mu\text{-}CH_2)(\mu\text{-}CO)Cp_2(CO)_2]$[10] does not react with sodium methoxide. **1** reacts with phenyllithium or $KHB[CH(CH_3)C_2H_5]_3$ to give respectively the IR spectroscopically characterized, polynuclear metalated acetophenone $Li^{\oplus}[Fe_n(CO)_m(CH_2COPh)]^{\ominus}$ **5** or acetaldehyde $K^{\oplus}[(Fe_n(CO)_m(CH_2CHO)]^{\ominus}$ **6**[8b].

Protolysis of **2** furnishes methyl acetate in high yields (ca. 50%); as expected, with deuterated acids such as CF_3COOD, methyl acetate monodeuterated in the acetyl function is formed. Reaction of **1** with methanol also leads to almost quantitative yields of methyl acetate[11]. A "base reaction mechanism" according to Scheme 1 also appears plausible for the reaction with alcohols.



Scheme 1.

Our findings would suggest at least an indirect interaction of the CH_2-bridge with a terminal CO ligand[2]; we thus may have a model here for explaining the formation of oxygen-containing products by the "methylene-oligomerization mechanism" in the Fischer-Tropsch synthesis[13].

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1, 73448-09-6; **3**, 36464-67-2; **4** (R = Me), 90194-64-2; **4** (R = *n*-Bu), 90171-77-0; PPNCl, 21050-13-5; $KHB[CH(CH_3)C_2H_5]_3$, 54575-49-4; $NaOCH_3$, 124-41-4; CH_3COOCH_3, 79-20-9; methyllithium, 917-54-4; butyllithium, 109-72-8; acetaldehyde, 75-07-0; acetone, 67-64-1; valeraldehyde, 110-62-3; hexanone, 591-78-6; phenyllithium, 591-51-5; monodeuterated methyl acetate 6181-03-9.

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[4] IR spectrum of **2** (in THF; $\tilde{\nu}$ [cm^{-1}]): $\nu_{CO(t)}$ 2005 vs, 1982 vs, 1972 vs, 1958 vs, 1920 sh, 1907 s, 1870 s; $\nu_{CO(b)}$ 1817 m, 1760 m; ν_{acyl} 1660 m.

[5] $PPN^{\oplus}[Fe_n(CO)_m(CH_2COOCH_3)]^{\ominus}$ **2a**: IR (THF; $\tilde{\nu}$ [cm^{-1}]): $\nu_{CO(t)}$ 2058 w, 1999 vs, 1985 vs, 1970 vs, 1946 vs, 1896 vs; $\nu_{CO(b)}$ 1815 sh, 1790 m, 1748 m; ν_{acyl} 1685 m. ^{1}H-NMR ([D$_6$]acetone, TMS int.): $\delta = 1.54$ (s, 2H), 3.37 (s, 3H), 7.61 (m, 30H).

[6] Procedure: A mixture of **1** (4.24 g, 12.1 mmol) and $NaOCH_3$ (0.64 g, 11.8 mmol) is treated with 50 mL anhydrous tetrahydrofuran under argon and stirred for 45 min at room temperature. After addition of 7.14 g (12.4 mmol) PPNCl the mixture is stirred for a further 2 h and filtered. After removal of THF the residue is taken up in 15 mL dimethyl sulfoxide (DMSO) and stirred for 18 h at 80 °C. The DMSO is removed under high vacuum, the residue extracted with 240 mL CH_2Cl_2/ether (1 : 5), and the extract evaporated to dryness. The residue is washed with ether until the washings appear almost colorless. The reddish white solid is dissolved in 30 mL CH_2Cl_2/ether (1 : 5), the solution filtered, and the filtrate cooled to 0 °C. Crystals of **3** slowly separate out. Fourfold repetition of this procedure furnishes analytically pure **3** as greenish yellow needle-like crystals (yield 13%, referred to $NaOCH_3$).—IR (KBr; $\tilde{\nu}$ [cm^{-1}]): ν_{CO} 2005 s, 1912 vs, 1891 vs, 1880 vs; ν_{acyl} 1680 s. ^{1}H-NMR

([D6]acetone, TMS int.): $\delta = 1.51$ (s, 2H), 3.40 (s, 3H), 7.66 (m, 30H). ^{13}C-NMR ([D6]acetone, TMS int.): $\delta = 1.49$ ($FeCH_2$), 49.51 (OCH_3), 127.13–134.52 (PPN), 184.09 (OCO), 221.63 (FeCO). M.p. 115°C (sealed tube, uncorrected). For an analogous compound $PPN^{\oplus}[(OC)_4Fe(CH_2COOC_2H_5]^{\ominus}$, prepared via an alternative route, cf. W. O. Siegl, J. P. Collmann, *J. Am. Chem. Soc. 94* (1972) 2516.

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Structure of a Novel μ_3-Oxo-$Fe_2^{III}Cr^{III}$-Glycine Complex**

By *William Clegg, O. Mi Lam,* and *Brian P. Straughan**

Several crystal structures have been determined for trinuclear oxo-centered carboxylates of vanadium[1], chromium[2], manganese[3], and iron[2]. Their structures are of great interest because mixed-valence species as well as mixed-metal triangular complexes have been confirmed. A key question in connection with the mixed-valence species is whether they show valence trapping or a symmetrical structure with equivalent metal atoms. No crystal structure has so far been determined for mixed-metal carboxylate systems of the type $(M_A^{III})_2M_B^{III}$.

The structure of the μ_3-oxo-Fe_3^{III}-alanine complex **1** is of biochemical interest as a model for the ferritin iron core[4]. The L-alanine in **1** is present as a zwitterion, and the nitrogen atoms are not involved in the iron-ligand bonding.

$[Fe_3(\mu_3\text{-}O)(\text{L-alanine})_6(H_2O)_3][ClO_4]_7 \cdot x\,H_2O$ **1**
$[Fe_2Cr(\mu_3\text{-}O)(\text{glycine})_6(H_2O)_3][ClO_4]_7 \cdot 6\,H_2O$ **2**

During the course of our own studies on metal complexes with carboxylates and amino acids, we found that very large (1–1.5 cm) deep red-brown crystals of **2** were deposited when a warm aqueous solution (60°C) of $Cr(ClO_4)_3$, $Fe(ClO_4)_3$, and glycine (molar ratio 1:2:6) was set aside with occasional maceration for a period of two months. Satisfactory elemental analyses (C, H, N, and Fe) were obtained, and a single-crystal X-ray diffraction study has confirmed the trinuclear structure (Fig. 1).

Examination of the structure of **2** and comparison with other *triangulo*-complexes lead to the following conclusions:

1) The Fe_2Cr-arrangement is *ordered* in the crystal structure of **2**, as indicated by the thermal parameters; refinement with three Fe atoms gives a considerably higher temperature factor for one atom. The four symmetry-equivalent cations in each unit cell are arranged such that all the Cr–(μ_3-O) bonds are aligned in two directions inclined at only 35.4° to each other. This alignment implies the presence of magnetic ordering.

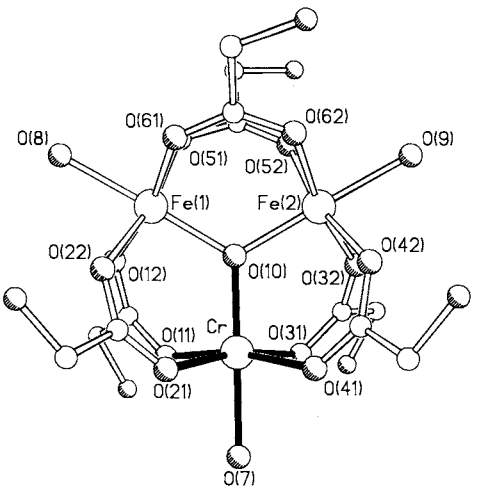

Fig. 1. Structure of the complex cation $[Fe_2Cr(\mu_3\text{-}O)(\text{glycine})_6(H_2O)_3]^{7+}$ of **2** in the crystal. Space group Cc, $a = 19.576(5)$, $b = 14.555(3)$, $c = 19.812(5)$ Å, $\beta = 106.80(2)°$, $Z = 4$, $R = 0.074$ for 6632 reflections with $F > 4\sigma(F)$. Key distances [Å]: Cr–O10 1.900(2), Fe1–O10 1.910(2), Fe2–O10 1.921(4), Cr–O7 2.043(9), Fe1–O8 2.053(6), Fe2–O9 2.079(7), Cr···Fe1 3.322(3), Cr···Fe2 3.288(3), Fe1···Fe2 3.316(3), mean Cr–O(glycine) 2.03(2), mean Fe–O(glycine) 2.01(1) Å. Further details on the crystal structure analysis can be obtained from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, by quoting the depository number CSD 50867, the names of the authors, and the journal citation.

2) Substitution of an Fe atom by a Cr atom in the cation introduces virtually no deviation from the ideal threefold symmetry in the central core. The less symmetrical arrangement of the glycine ligands is a consequence of the lower symmetry of the overall crystal structure.

3) The triangular structure of these complexes is largely independent of the precise nature of the other oxygen-containing ligands coordinated to the trinuclear unit (carboxylate, amino acid, water, etc.) and of the nature of the counterion ($ClO_4^{\ominus}$, $NO_3^{\ominus}$, etc.).

The $Fe_2Cr(\mu_3\text{-}O)$-glycine complex **2** has an average M···M separation of 3.309(3) Å. An interesting comparison can be made with analogous acetate complexes of Cr^{III} and Fe^{III}[2]. Crystal structure data for these indicate very similar average M···M distances, in the range 3.274–3.307 Å. Mixed-valence analogues (M^{II}/M_2^{III}) of ruthenium[5], chromium[6], and manganese[7] exhibit slightly longer average M···M distances, in the range 3.329–3.363 Å. In the absence of direct metal-metal bonding, the central geometry of these complexes seems to be dictated mainly by the size of the (μ_3-O) atom. In contrast, the average M···M distance in $[Pd_3^{II}(\text{acetate})_6]0.5\,H_2O$[8], a complex with no central oxygen atom, is only 3.15 Å, even though there is no recognized formal direct metal-metal interaction. For doubly oxo-capped trinuclear structures of molybdenum[9] and tungsten[10] with acknowledged metal-metal interactions, the M–M bond lengths are considerably shorter (2.766 and 2.745 Å, respectively), and the presence of a central in-plane oxygen atom is presumably impossible for steric reasons.

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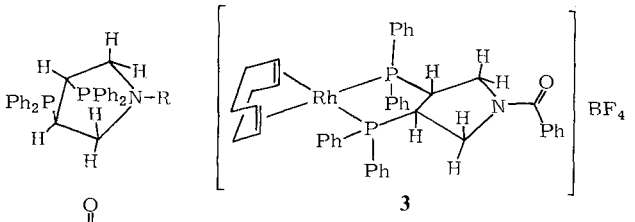
Asymmetric Hydrogenation of α-(Acetylamino)cinnamic Acid with a Novel Rhodium Complex; the Design of an Optimal Ligand**

By *Ulrich Nagel**

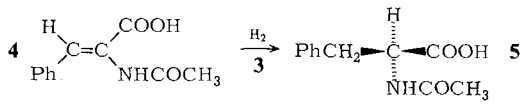
Rhodium complexes of optically active bisphosphanes facilitate the asymmetric hydrogenation of prochiral olefins, in some cases in high optical yields[1]. The new 1,2-bisphosphane **1** (benzoylpyrphos) is presented here as a ligand especially suited for the hydrogenation of α-(acylamino)acrylic acids to (*S*)-*N*-acylamino acids.



3

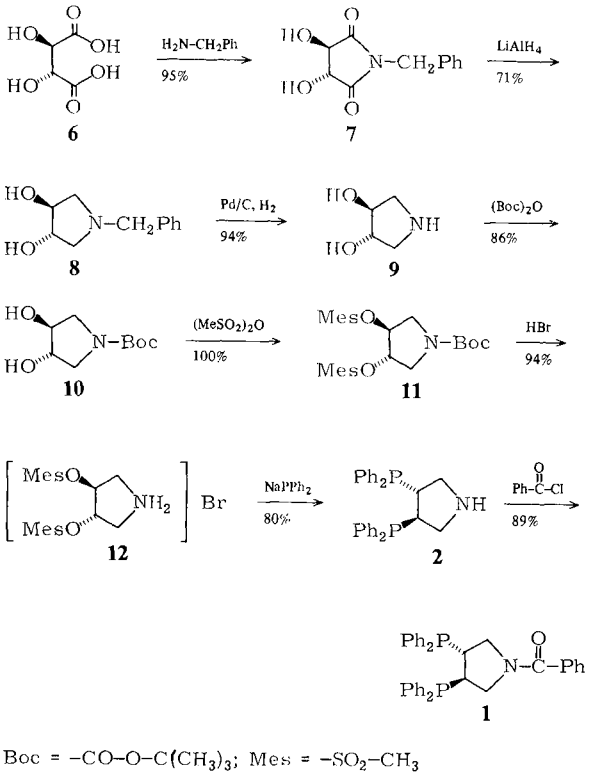
1, R = $-\overset{O}{\overset{\|}{C}}-Ph$
2, R = H

The novel rhodium complex {(*R,R*)-*P,P'*-[*N*-benzoylpyrrolidine-3,4-diyl]bis(diphenylphosphane)}-1,5-cyclooctadienerhodium tetrafluoroborate **3** catalyzes the hydrogenation of α-(acetylamino)cinnamic acid **4** to (*S*)-*N*-acetylphenylalanine **5** with 99% *ee*. In contrast to hydrogenations with other enantioselective catalysts, this hydrogenation can be carried out under pressure without loss of selectivity. The reaction rate increases linearly with the hydrogen pressure (0.8 min^{-1} at 1 bar, 40 min^{-1} at 50 bar). Even high substrate to catalyst ratios (10000 : 1) can be used without lowering the selectivity and, at 50 bar hydrogen pressure, such conversions are achievable in only 10 h.



All structural units known to increase the optical yield in the hydrogenation of acryl acid derivatives were incorporated in the ligand **1**. The ligand is chemically stable under the conditions used for the catalysis. It does not contain any P–O or P–N bonds, which undergo solvolysis on prolonged reaction[2], and it imposes a markedly rigid conformation (λ-conformation) on the five-membered metallacycle[3].

Variation of the substituents on the nitrogen atom of **1** has no marked influence on the catalytic activity and the selectivity of the resulting rhodium complex. Only in the case of **2** (R = H) is the catalytic hydrogenation slower, which could be due to an oxidative addition of N–H to Rh^I. Even substituents on the phenyl group of **4** have little influence on the optical yield; thus, e.g., the 4-hydroxy-, 4-methoxy-, 4-hydroxy-3-methoxy-, or 3,4-methylenedioxy-derivatives all give over 95% *ee*.



Boc = $-CO-O-C(CH_3)_3$; Mes = $-SO_2-CH_3$

Scheme 1.

1 was obtained in eight steps from natural (*R,R*)-(+)-tartaric acid **6** (overall yield 36%) (Scheme 1). Attempts to prepare (*S,S*)-3,4-dihydroxypyrrolidine **9** via the tartrimide met without success; *N*-benzyltartrimide was therefore used. The Boc-moiety in **11**, which was obtained via the sequence **7** → **8** → **9** → **10** → **11**, must be removed since reaction of **11** with sodium diphenyl phosphide leads to elimination products. The reaction of **12** is critical and only affords satisfactory yields when carried out in dimethylformamide (DMF)[5].—So far the only optically active 3,4-dihydroxypyrrolidine described in the literature since we completed our studies has been the *N*-phenyl derivative[2].

A particular advantage of the new ligand is that the *N*-substituent can be varied, i.e. the ligand itself can be tailored according to its intended use. Two polymer-bound chiral bisphosphanes (DIOP and PPM) are known[1,4].

Preliminary experiments with **2** bonded to Merrifield resin or silica gel furnished heterogeneous catalysts which hydrogenate **4** in methanol with 95% *ee*—an enantioselectivity which has so far never been achieved in heterogene-

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ous catalysis. The hydrogenation with the silica-bound catalyst is only slightly slower than in solution; after filtration, the catalyst could even be used again without reducing the selectivity.

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[5] Procedure: A solution of $NaPPh_2 \cdot 2$ dioxane (10.5 g, 27.5 mmol) in DMF (60 mL) is treated at −35 °C with 2.6 g (7.6 mmol) **12** and the mixture stirred for ca. 12 h at −12 °C. After removal of the solvent, dissolution of the residue in water, and extraction of the aqueous solution with ether, 2 N HCl is added to the ether extract to precipitate **2** as the hydrochloride. Treatment of **2** with benzoyl chloride affords **1** [colorless, m.p. 180—182 °C; $[\alpha]_D^{22}$ +153 (c = 2.84, toluene), reprecipitation from toluene/hexane]. **1** reacts with $[Rh(cod)_2]BF_4$ to give **3** [yellow, readily soluble in methanol, reprecipitation with ether]. Typical experiment: A solution of **4** (2.05 g, 10 mmol) in methanol (30 mL) was treated with 1 mg (0.0012 mmol) **3** and the mixture stirred in a 50 mL steel autoclave under an average pressure of 40 bar H_2 (ca. 12 h at RT). After addition of 1 mL 0.1 N HCl, the solution was evaporated to dryness, the residue taken up in NaOH, and the catalyst removed by extraction with dichloromethane. The aqueous solution was acidified and extracted with ethyl acetate. After removal of the ethyl acetate, pure **5** was obtained in quantitative yield. According to polarimetric measurements the optical purity was 99%; the rotation of a recrystallized sample agreed to within 0.1 with the value quoted in the literature [6] $[\alpha]_D^{20}$ +47.4 (c = 1.95%, ethanol), and was taken as reference.
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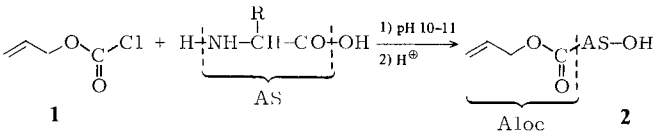
The Allyloxycarbonyl (Aloc) Moiety—Conversion of an Unsuitable into a Valuable Amino Protecting Group for Peptide Synthesis**

By *Horst Kunz** and *Carlo Unverzagt*

For the synthesis of sensitive peptides and glycopeptides, we have used the allyl moiety to block carboxy groups reversibly[1,2]. This protecting group can be rapidly removed under mild, practically neutral conditions either via rhodium(I)-catalyzed isomerization[3] or by palladium(0)-catalyzed allyl transfer[4]. In attempting to use these advantageous properties also for the protection of the *N*-terminal group, we became aware of the allyloxycarbonyl (Aloc) protecting group, which *Stevens* and *Watanabe*[5] investigated with D,L-amino acids. These authors established that hydrogenolytic cleavage of the Aloc moiety leads to marked hydrogenation, forming noncleavable propoxycarbonyl groups. Also, reduction with sodium in liquid ammonia (yield 65—85%) and cleavage with phosphonium iodide in glacial acetic acid (yield 70—75%) affords only incomplete deblocking. The Aloc moiety therefore appeared to be less than suitable for peptide synthesis[6].

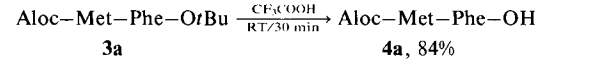
We have now found, however, that the combination of the Aloc amino-protecting group with a novel cleavage method is highly propitious.

Although the Aloc moiety can be introduced using the allyl chloroformate **1** under Schotten-Baumann conditions[5], it is more advantageous to use the pH-stat method at pH 10—11. The Aloc-amino acids **2** (**2c** forms a crystalline hydrate, m.p. = 52 °C), which are generally oily, were identified by elemental analysis and by ^{1}H-NMR spectroscopy[7]. The advantage of the small Aloc protecting group is demonstrated by the condensation reactions. In the presence of ethyl-2-ethoxy-1,2-dihydroquinoline-1-carboxylate (EEDQ)[8], Aloc-amino acids **2** react with *tert*-butyl amino acid esters to afford the Aloc-dipeptide *tert*-butyl esters **3** in high yield.



1 **2**

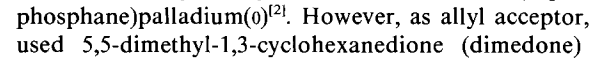
2a, AS = Phe, 84%; **2b**, AS = Met, 80%;
2c, AS = Ser, 79%; **2d**, AS = Ala, 77%



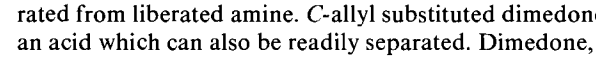
2 **3**

3a, AS–AS′ = Met–Phe, 92%
3b, AS–AS′ = Phe–Ser(*t*Bu), 95%
3c, AS–AS′ = Ala–Ser(*t*Bu), 94%

The *tert*-butyl esters **3** can be smoothly and selectively decomposed with trifluoroacetic acid, without the Aloc group being attacked. The latter group survives even the considerably lengthened reaction times required for the complete cleavage of the *tert*-butyl ether of serine.



3a **4a**, 84%

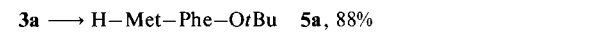


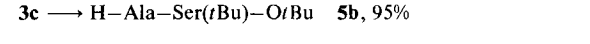
3b **4b**, 83%

For the cleavage of the Aloc moiety from the esters **3**, we chose catalytic allyl transfer with tetrakis(triphenylphosphane)palladium(0)[2]. However, as allyl acceptor, we used 5,5-dimethyl-1,3-cyclohexanedione (dimedone) instead of morpholine.

The CH-acid dimedone (pK_a = 5.2) can readily be separated from liberated amine. *C*-allyl substituted dimedone is an acid which can also be readily separated. Dimedone, especially if it is used in a 7- to 8-fold excess, protonates the free amino function ($pK_a \approx 8$) to such an extent that the latter can neither function as an allyl acceptor nor is able to form an enamine with dimedone within the reaction time[9].

By means of this method[10], the Aloc protecting group can be completely removed from the dipeptide esters **3** in 30 min in tetrahydrofuran (THF) at room temperature using 5–10 mol-% of catalyst.





The thioether function of methionine influences neither the activity of the palladium catalyst nor is itself alkylated. The very mild and highly selective deblocking method is therefore widely applicable.

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The advantages of the small allyloxycarbonyl (Aloc) protecting group are demonstrated by the high yield (95%) in which the protected tetrapeptide *tert*-butyl ester Aloc–Met–Phe–Ala–Ser(*t*Bu)–O*t*Bu, is obtained from **4a** and **5b** in THF with EEDQ. By virtue of the cleavage method described here, the long-known allyloxycarbonyl (Aloc) moiety has become transformed into an effective and highly selective tool for the synthesis of sensitive peptide derivatives.

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[7] $[\alpha]_D^{22}$ ($c=1$, $CHCl_3$): **2a**: +35.8; **2b**: +10.2; **2c** (in H_2O): −6.0. ^{1}H-NMR ($CDCl_3$): Allyl-H in **2a**–**c** ($CDCl_3$): $\delta=5.9$ (ddt, $J_{cis}=10$ Hz, $J_{trans}=17$ Hz, $J_{vic}=5$ Hz, 1H, −CH=), 5.25 (dd, $J_{trans}=17$ Hz, $J_{gem}\approx 1$ Hz, $^4J<1$ Hz, 1H, =CH(*trans*)); 5.18 (dd, $J_{cis}=10$ Hz, $J_{gem}\approx 1$ Hz, $^4J<1$ Hz, 1H, =CH(*cis*)); 4.55 (m, 2H, $-CH_2-$).
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[10] Procedure: L-Methionyl-L-phenylalanine-*tert*-butyl ester **5a**: Tetrakis(triphenylphosphane)palladium(0) (0.15 g, 0.13 mmol) and dimedone (1.4 g, 10 mmol) are added to a solution of **3a** (0.57 g, 1.32 mmol) in 10 mL THF under argon. The mixture is stirred for 30 min, the solvent distilled off in vacuo, the residue taken up in 100 mL ether, filtered, and extracted with 0.5 N HCl (4 × 50 mL). The combined aqueous phases are adjusted to pH 10 with Na_2CO_3 and extracted with ether (4 × 100 mL). After the ether solution is dried over Na_2SO_4, the ether is distilled off in vacuo and **5a** is obtained as an analytically pure oil. Yield 0.41 g (88%), $[\alpha]_D^{22}$ +29.4 ($c=1$, $CHCl_3$) (ref. [11]: +29.6 ($c=1$, $CHCl_3$)).
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Transfer of Chirality in the Addition of Chiral α-Chloroallylboronate Esters to Aldehydes**

By *Reinhard W. Hoffmann** and *Bernd Landmann*

Optically active homoallyl alcohols have previously been prepared in moderate to excellent enantiomeric purity by addition of chirally modified allylmetal compounds to aldehydes[1]. An attractive route to these compounds is presented by the use of chiral α-substituted allylmetal compounds, which upon addition to aldehydes transfer the chirality to the newly formed stereocenter[2]. The sign and extent of the transfer of chirality depend to what extent the reaction proceeds uniformly via one of several stereoisomeric transition states (e.g. **5** or **6**)[3]. We report here on the addition of chiral α-chloroallylboronates **4** to aldehydes, which leads to homoallyl alcohols **8** with ≥90% transfer of chirality.

Chiral α-substituted boronic esters are accessible using the method described by *Matteson* et al.[4]. Thus, the cyclic dichloromethaneboronate **1** derived from (*R,R*)-2,3-butanediol was allowed to react with vinylmagnesium chloride and $ZnCl_2$ to give the α-chloroallylboronate **2**. Its diastereomeric purity could not be ascertained from the ^{13}C-NMR spectrum, but should be ≥90% (vide infra). The absolute configuration of **2** was determined as (*S*) by converting it into the 2,3-pinanediyl ester **3**, whose ^{1}H-NMR spectrum differs in a known and characteristic way from that of the diastereomer[5].

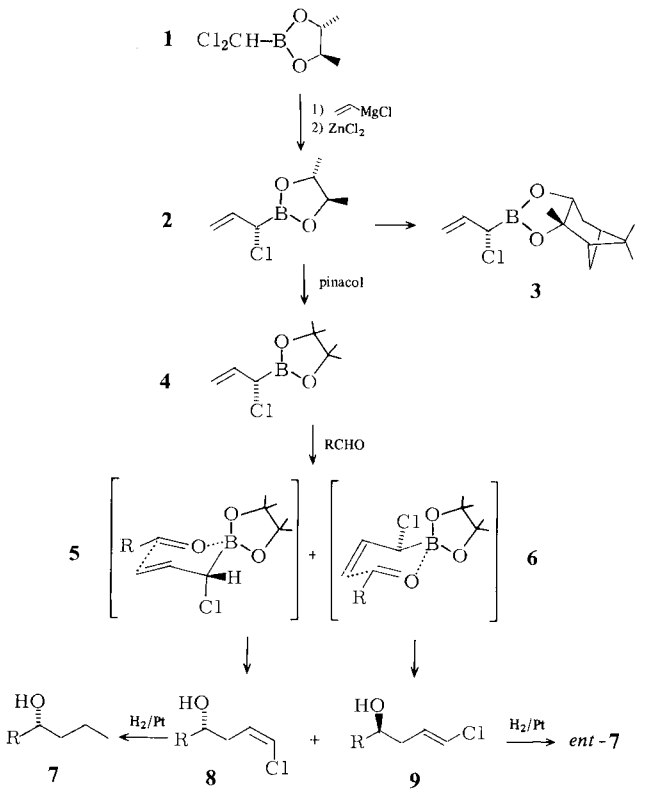

Table 1. Formation of **8** and **9** from **4** and aldehydes: conversion of **8** into **7**. *o.p.* = optical purity

	R	**8** : **9**	**8**: *ee* [%]	**7**: Conf. [a]	*o.p.* [%]
a	CH_3	93:7	90–93	*S*	—
b	C_2H_5	94:6	90–93	*S*	76
c	$(CH_3)_2CH$	96:4	90–93	*R*	—
d	C_6H_5	95:5	90–93	*R*	76

[a] Determined from the rotation value of **7**.

In order to achieve a high *Z/E*-ratio of the products **8/9** in the addition of **2** to aldehydes[6], **2** was first converted into the pinacol ester **4**. The latter, as previously described for the racemic series[6], adds to aldehydes (cf. Table 1) to give homoallyl alcohols (**1** → **8**, **9**) in an overall yield of ca. 50%. The enantiomeric purity of the major component **8** was determined from the ^{19}F-NMR spectra after esterification with Mosher's reagent. The absolute configuration of **8** was obtained by converting it into the known alcohols **7** via hydrogenolysis of the C–Cl bond and hydrogenation of the double bond on Pt/C in methanolic KOH[7].

The relative configuration of the educt **4** and product **8** are once again[3] in accord with the reaction proceeding via a cyclic six-membered transition state **5** in the chair conformation. Inasmuch as the by-product **9**, with *E*-configurated double bond, is formed via the same type of transition state, i.e. **6**, the new center of chirality in **9** must exhibit the opposite configuration to that of **8**. This becomes notable, e.g., if the double bond is removed or cleaved[8]. In this way, hydrogenation of the diastereomeric pair **8/9** leads to an enantiomeric pair **7**/*ent*-**7**. For example, the phenyl derivative **7d**, obtained from **8d/9d**, had a lower enantiomeric purity (76%) than that of the starting material **8d**. The *Z/E*-ratio of the homoallyl alcohols **8/9** is there-

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fore decisive for the enantiomeric purity of the products derived therefrom, and hence in this respect efforts at improvement must be made. In contrast, the problem of obtaining educts **4** in high enantiomeric purity can be regarded as being solved: The constant *ee* values of 90—93% for **8a—d** prove that **4** exhibits at least this *ee*-value. Furthermore, the constancy of the *ee*-value for the compounds **8** examined indicates that the transfer of chirality from **4** to **8** is cogent.

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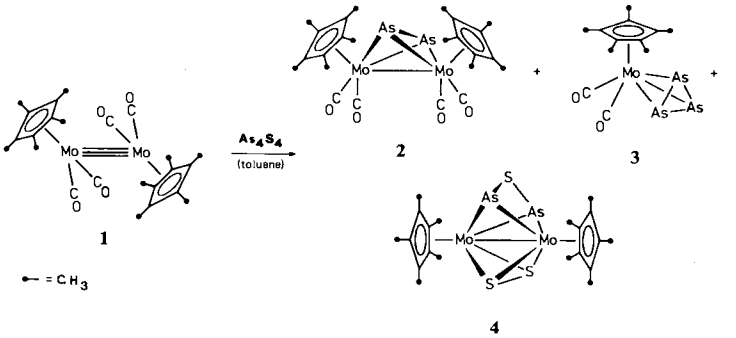
Ligand Extrusion from the As_4S_4-Cage by $[C_5Me_5(CO)_2Mo]_2$: Formation of $(C_5Me_5)_2Mo_2(CO)_4(\mu,\eta^2\text{-}As_2)$, $C_5Me_5(CO)_2Mo(\eta^3\text{-}As_3)$, and $(C_5Me_5)_2Mo_2As_2S_3$**

By *Ivan Bernal, Henri Brunner, Walter Meier, Heike Pfisterer, Joachim Wachter**, and *Manfred L. Ziegler*

The chalcogenide-rich binuclear complexes of the type $(C_5Me_5)_2Mo_2X_4$ (X = S, Se) can be prepared by complete exchange of the CO groups of $[C_5Me_5(CO)_2Mo]_2$ **1**, which contains one Mo≡Mo bond, by reaction with elemental sulfur or selenium[1]. Since a similar synthetic principle has also been found for $(C_5H_5)_2Mo_2As_5$, a combination of arsenic with sulfur or selenium should lead to previously unknown arsenide/chalcogenide ligands. In fact, realgar (As_4S_4), which is moderately soluble in organic solvents, proves to be a suitable synthetic reagent. Surprisingly, reaction of As_4S_4 with **1** also gives rise to a η^3-As_3 complex which belongs to the still less researched monosubstituted derivatives of yellow arsenic.

The two arsenic-containing complexes **2** and **3** as well as the arsenic- and sulfur-containing complex **4** are formed by heating an equimolar mixture of **1** and As_4S_4 in toluene[3]; no complex containing only sulfur could be detected. The compositions of all the products have been verified by elemental analysis (C, H, As, S) and mass spectroscopy. The spectroscopic data of **2** [IR: ν_{CO} = 1976, 1913, 1897, 1823 cm^{-1} (toluene solution); ^{1}H-NMR: δ_{CH_3} = 1.98 ($CDCl_3$)] indicate a tetrahedral Mo_2As_2 cluster, as previously established by X-ray crystallography for $(C_5H_5)_2Mo_2(CO)_4(\mu,\eta^2\text{-}As_2)$[4].



X-Ray structure analysis of **3**[5] indicates that the Mo atom forms the apex of a tetrahedron with a practically equilateral As_3 triangle as base (cf. Fig. 1). A crystallographically stipulated mirror plane through the atoms As1, Mo, C2, and C3 bisects the bonds As2—As2′ and C6—C6′ as well as the angle C1—Mo—C1′. Just as in $As_3Co(CO)_3$, the As—As distances (2.375 Å) are shorter than in the free As_4 molecule[6]. In order to account for this result, a reduction in the mutual repulsion of the lone pairs of electrons by transfer of electron density to the central metal atom and the other ligands[6] or an increase in bonding and a decrease in antibonding interactions within the As_3-ring by coordination to the metal[7] have been postulated.

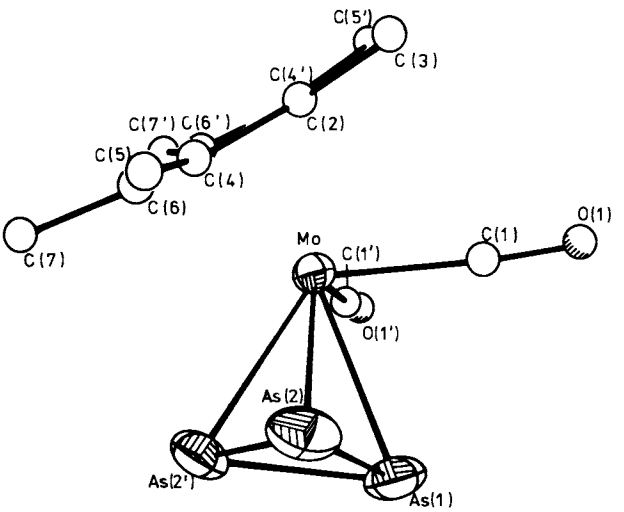


Fig. 1. Molecular structure of the complex **3** in the crystal (ORTEP representation). Selected bond lengths [pm] and angles [°]: Mo—As1 270.6(2), Mo—As2 263.9(1), Mo—C1 200.7(7), Mo—C2 227(1), Mo—C4 233(1), Mo—C6 239(1), As1—As2′ 237.2(1), As2—As2′ 237.7(2); As2—Mo—C1 87.4(2), C1—Mo—C1′ 90.5(4), C_5Me_5(cent)—Mo—As_3(cent) 136(2), C_5Me_5(cent)—Mo—C1 96.4(4), As_3(cent)—Mo—C1 113.5(2), As2—As1—As2′ 60.2(1), As1—As2—As2′ 59.9(0).

Experimental proof for an increased charge density at the central metal is provided, for the first time, for **3** by comparison with the isoelectronic complex $C_5Me_5Mo(CO)_2NO$[8]. Correspondingly, in **3** a more "obli-

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[**] Reactivity of the M-M Multiple Bond in Metal Carbonyl Derivatives, Part 9. – Part 8: J. Wachter, J. G. Riess, A. Mitschler, *Organometallics*, in press.

quely" arranged C_5Me_5-ring is found in which the distances of the atoms C6 and C6′, which are *cis* to the As_3-ligand, to Mo are ca. 0.12 Å more than that of C2, and the Mo–C distances for the CO ligands are at least ca. 0.065 Å longer. The ν_{CO} frequencies in **3** [1964, 1904 cm^{-1} (KBr)], which are over 20 cm^{-1} lower, are consistent with this.

To date, single crystals of the air-sensitive, red-violet complex **4** have eluded isolation. In addition, the IR spectrum—weak absorptions at 422 and 388 cm^{-1} suggest Mo-ligand bridging functions—cannot be interpreted in more detail; nevertheless the ^{1}H-NMR spectrum [$\delta_{CH_3}=2.03$ in $CDCl_3$/[D_8]toluene (1:2) at −26 °C] indicates a symmetric structure. By analogy to the previously known structures of $(C_5Me_5)_2Mo_2(\mu,\eta^2\text{-}S_2)(\mu\text{-}S)_2$[1a] and $(C_5Me_5)_2Mo_2(\mu,\eta^2\text{-}As_3)(\mu,\eta^2\text{-}As_2)$[2], **4** probably contains a μ,η^2-AsSAs and a μ,η^2-S_2 ligand, which should both lie in a plane between the two Mo atoms. The sum of valence electrons from all the ligands therefore amounts to 10 per Mo atom, which enables the latter to attain the nobel gas configuration upon inclusion of the corresponding metal d-orbitals. This scheme is corroborated by studies on the reactivity. Thus, no weakly bonded sulfur is eliminated by PPh_3, for example, and, even under mild conditions, S_8 displaces the As_2S ligand to form the blue complex $(C_5Me_5)_2Mo_2(\mu,\eta^2\text{-}S_2)(\mu\text{-}S)_2$[1a].

No statements can be made at present about the mechanism of fragmentation of the As_4S_4-cage since the complexation of intact realgar has not yet proved possible. However, the novel compounds **2**–**4** appear to be relatively thermodynamically stable, as also indicated by the decomposition of the structurally totally different P_4S_3 into $C_5Me_5(CO)_2MoP_3$, $(C_5Me_5)_2Mo_2P_2S_3$, etc.[9].

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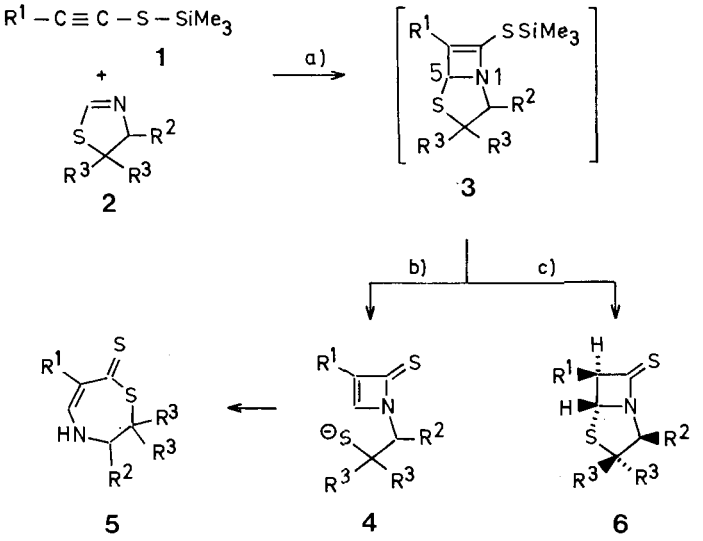
Thiopenam Derivatives from Alkynyl Silyl Sulfides and 4,5-Dihydrothiazoles**

By *Ernst Schaumann**, *Wolf-Rüdiger Förster*, and *Gunadi Adiwidjaja*

Although β-lactam antibiotics have been modified in a variety of ways[1], the replacement of the oxo group in the four-membered ring by hetero-substituents has so far not been studied in detail. As previously described in the literature, a tosylimino group can easily be introduced[2], whereas the sulfuration of biologically active β-lactams



Scheme 1. a) 20 °C, 7 d, without solvent; b) H_2O, CsF or SiO_2; c) Ultrasonication (20 min), then H_2O.

	R^1	R^2	R^3		R^1	R^2	R^3
1a	*t*Bu			**5a, 6a**	*t*Bu	H	H
1b	Ph			**5b**	Ph	H	H
2a		H	H	**5c**	*t*Bu	COOMe	H
2b		COOMe	H	**5d, 6b**	*t*Bu	COOMe	Me
2c		COOMe	Me	**5e**	Ph	COOMe	Me

gives only poor yields of the desired sulfurated products[3]. We have now investigated the possibility of obtaining β-thiolactams as part of a penicillin skeleton ("thiopenam derivatives") by reaction of the readily accessible alkynyl silyl sulfides **1a**, **b**[4], which are highly reactive toward nucleophiles, with the 4,5-dihydrothiazoles **2a**, **b** and (*S*)-**2c**[5].

The alkynes **1** react with the heterocycles **2** at room temperature to give adducts which may be formulated as silylthio derivatives **3**. Desilylation by hydrolysis, cesium fluoride or silica gel does not furnish the thiopenam system **6**, but leads, with cleavage of the S4–C5 bond, via **4** to dihydro-1,4-thiazepinethiones **5**.

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[3] An equimolar mixture (1.60 mmol) of $[C_5Me_5(CO)_2Mo]_2$ **1** and As_4S_4 in 100 mL of toluene is stirred for 17 h at 100 °C. After being concentrated to 10 mL, the mixture is filtered and chromatographed on SiO_2 (column 30 × 4 cm). An orange and a dark-red zone are eluted with toluene. Low pressure chromatography (Merck LiChroprep Si60) of the orange zone with toluene/pentane (1:2) as eluent afforded yellow **3** and orange **2** in 12 and 4% yield, respectively. Analytically pure **4** is obtained in 26% yield from the dark-red zone by washing the red-violet crude product with pentane (2 × 10 mL) and chromatography on SiO_2 using toluene/pentane (2:1) as eluent. The complexes **2**, **3**, and **4** can be recrystallized from Et_2O/pentane (3:1) and toluene/pentane (3:1), respectively.

[4] P. J. Sullivan, A. L. Rheingold, *Organometallics 1* (1982) 1547.

[5] **3** crystallizes rhombohedrally, D_{2h}^{16}-Pnam, $a=861.1(2)$, $b=1334.7(5)$, $c=1355.7(5)$ pm, $V=1558.1\times10^6$ pm^3, $Z=8$. Syntex diffractometer ($Mo_{K\alpha}$), $3°\leq2\theta\leq55°$, 1015 absorption-corrected reflections, Patterson (Mo, As) and Fourier methods, anisotropic refinement to $R_w=2.7\%$. Further details on the crystal structure investigation can be obtained from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, by quoting the depository number CSD 50808, the names of the authors, and the journal citation.

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[9] The reaction of P_4S_3 with **1** proceeds under the same conditions as that of As_4S_4; we were able to isolate $(C_5Me_5)_2Mo_2P_4S$ as additional product (unpublished results).

Table 1. Yields, melting points and some NMR data of the compounds **5** and **6**.

Product	Yield [%]	M.p. [°C]	NMR [a] δ(=CH)	δ(H-5)	δ(H-6)	δ(^{13}C=S)
5a	60	123	6.89 (d, 8.4)	—	—	217.5 [b]
5b	77	150	6.89 (d, 9)	—	—	212.7 [b]
5c	74	oil	6.97 (d, 9) [b]	—	—	[c]
5d	50	135	7.05 (br. s)	—	—	[c]
5e	79	129 (dec.)	7.03 (d, 9)	—	—	[c]
6a	80	oil	—	2.82 (d, 1.5)	5.13 (d, 1.5)	215.0
6b	55	64	—	2.93 (d, 1.2)	5.53 (d, 1.2)	212.2

[a] Including the multiplicity, $^3J_{HH}$ [Hz]; in $CDCl_3$, if not otherwise stated. [b] In $(CD_3)_2SO$. [c] Not measured.

For penicillins, this rearrangement is already well-known[6]. However, the ring-opening can be suppressed if the *tert*-butylsubstituted sulfide **1a** is used as starting material and the reaction mixture is concomitantly treated with cesium fluoride and subjected to ultrasonication. The constitution of the stereochemically uniform thiopenam compounds **6a** and **6b** obtained with **2a** and (*S*)-**2c**, respectively, is confirmed by the spectroscopic data (Table 1) and by an X-ray structure analysis of **6b** (Fig. 1)[7].

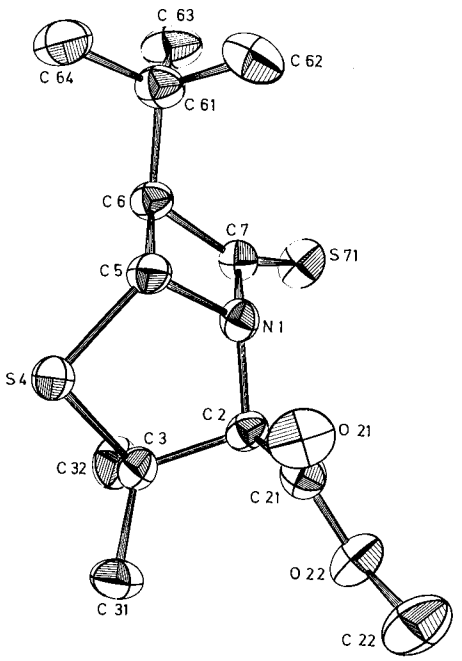

Fig. 1. ORTEP plot of the structure of **6b** in the crystal. Selected bond lengths [pm] and angles [°] (average values of two independent molecules): N1–C5 146.8(4), N1–C7 136.3(4), C6–C7 152.7(5), C7–S71 162.6(3); C5–N1–C7 95.6(3), N1–C7–C6 92.0(2).

The X-ray structure analysis shows that the carboxylic function and H-5 are *cis*-oriented, as in natural penicillins, whereas H-5 and H-6 are arranged *trans* to each other, as also indicated by the relatively small $^3J_{HH}$ coupling (Table 1); thus, the whole molecule has a (2*S*,5*R*,6*R*)-configuration. The N1–C7 distance (136.3(4) pm) is shorter than the average value (139.5 ± 2.6 pm[8]) found on X-ray spectroscopic analysis of 33 penam derivatives. The higher ring strain implied by this finding is further supported by a flatter nitrogen pyramid: the distance from N1 to the C2–C5–C7 plane (3.61 pm) is smaller than in the corresponding β-lactam derivatives (average distance 3.94 pm[8]).

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[6] Review: R. J. Stoodley, *Tetrahedron 31* (1975) 2321.
[7] Crystal data: hexagonal, R3, $a = 2773.4(1)$, $c = 1081.7(1)$ pm, $Z = 18$ (2 independent, stereochemically identical molecules); $Cu_{K\alpha}$ radiation, 2150 independent reflections $2° \leq \vartheta \leq 60°$, $F_0 > 3\sigma$). Structure solved by MULTAN and Fourier methods; refinement without H atoms of the methyl groups: $R = 0.035$, $R_w = 0.035$. Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD 50780, the names of the authors, and the journal citation.
[8] Utilization of the Cambridge Crystallographic Data Files; cf. F. H. Allen, S. Bellard, M. D. Brice, B. A. Cartwright, A. Doubleday, H. Higgs, T. Hummelink, B. G. Hummelink-Peters, O. Kennard, W. D. S. Motherwell, J. R. Rodgers, D. G. Watson, *Acta Crystallogr. B35* (1979) 2331.

A Photochemical Entry to Macrocyclic Mono- and Dilactones**

By *Gerhard Quinkert**, *Gerd Fischer, Uta-Maria Billhardt, Jürgen Glenneberg, Ulrich Hertz, Gerd Dürner, Erich F. Paulus,* and *Jan W. Bats*

Dedicated to Professor Jan Thesing on the occasion of his 60th birthday

On irradiation of 2,4-cyclohexadien-1-ones at low temperature the resulting dienylketenes can be trapped and identified spectroscopically[1], provided any strong nucleophile is absent. If not, the characteristic UV/VIS spectrum of the dienylketene in question is superseded by a new absorption (see Fig. 1).

If the strong nucleophile is protic, the respective carboxylic acid derivative is formed. If, however, the strong nucleophile is aprotic, it may promote the reaction of an additionally present weak protic nucleophile which alone would not form the corresponding carboxylic acid derivative (see Figs. 2 and 3).

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[**] This work was supported by the Deutsche Forschungsgemeinschaft, by the Fonds der Chemischen Industrie, and by Hoechst AG.—Abbreviations: DABCO = 1,4-diazabicyclo[2.2.2]octane; MOM = methoxymethyl; THP = tetrahydropyranyl; TFE = 2,2,2-trifluoroethanol.

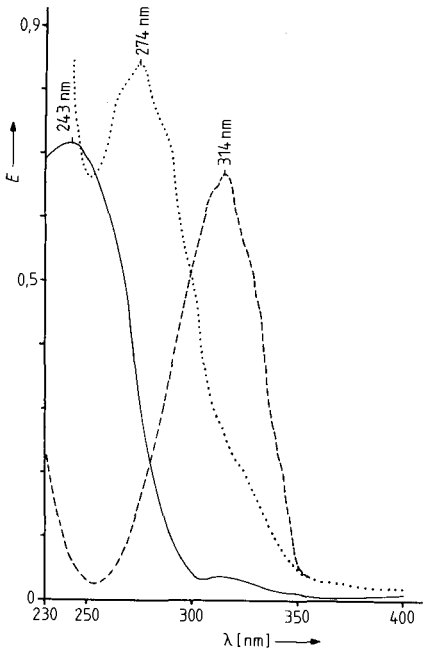


Fig. 1. UV/VIS spectra (at −90 °C in methylcyclohexane/isopentane (1 : 4)). Before irradiation of **1** (8.56×10^{-5} M) with 313 nm light (---); after irradiation of **1** with 313 nm light in the absence of DABCO (—); after irradiation of **1** (8.36×10^{-5} M) with 313 nm light in the presence of DABCO (· · ·).

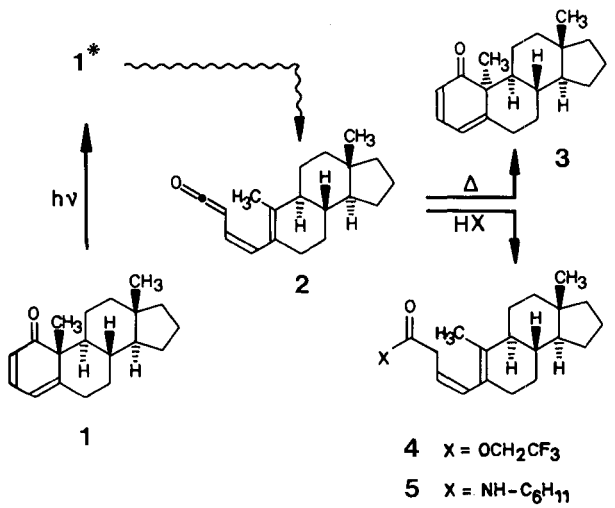


Fig. 2. Photoepimerization (to give **3** in TFE) or adduct formation (to give **4** in TFE after addition of DABCO in the molar ratio 1 : 12 or to give **5** in ether after addition of cyclohexylamine in the molar ratio 1 : 110 instead of DABCO) on exposure of **1** to light of wavelengths > 340 nm.

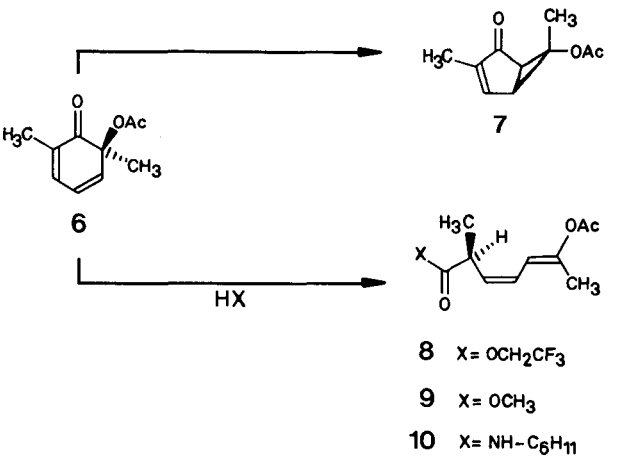


Fig. 3. Photocyclization (to give *rac*-**7** in TFE) or photochemical adduct formation (to give *rac*-**8** in TFE after addition of DABCO in the molar ratio 1 : 1.2 or to give *rac*-**9** in methanol or *rac*-**10** in ether in the presence of cyclohexylamine in the molar ratio 1 : 21) on exposure of *rac*-**6** to light of wavelengths > 340 nm.

When an ethereal solution of *rac*-**11a**[3] is irradiated with light of wavelength > 340 nm in the presence of DABCO (molar ratio 1 : 1.3-5), the 22-membered dilactone **14**[14] is formed in almost 30% yield, and the 33-membered trilactone **15**[3] in a good 6% yield. Under the same reaction conditions, *rac*-**11c**[5] furnishes the 16-membered monolactone *rac*-**13a** in almost 30% yield[6]. That the new method of cyclization can lead to the formation of macrolides in remarkably high yield (73%) is indicated by the conversion of *rac*-**11e** into *rac*-**13b**[7]. Constitution, ligand-orientation at the CC double bonds, and conformation of *rac*-**13a** and **14** have each been determined by single-crystal structure analysis[8-10]. The UV, IR, and NMR data of *rac*-**13a**, *rac*-**13b**, and **14** support the constitution and relative configuration formulated in Scheme 1.

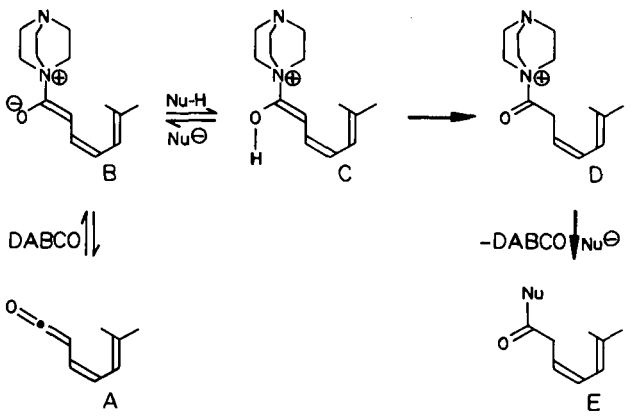
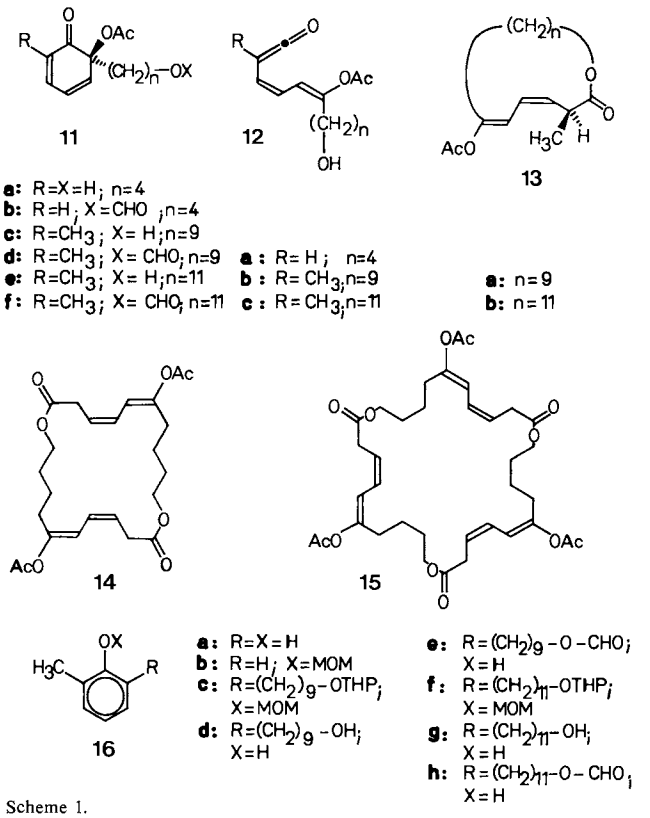


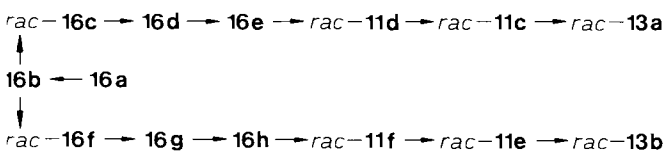
Fig. 4. DABCO-activated addition of a weak protic nucleophile (Nu–H) to a dienylketene. A: dienylketene; B: zwitterionic adduct of DABCO and A, which causes the new absorption (see Fig. 1); C: enol of D formed on uptake of a proton (from Nu–H); D: extremely reactive acylammonium compound; E: carboxylic acid derivative formed on replacement of DABCO by $Nu^{\ominus}$ (possibly also after deprotonation of Nu–H by DABCO).

DABCO is an efficient reagent for this purpose[2]. It activates the appropriate ketene (and perhaps also the protic addendum). The acylammonium compound expected to be formed finally, reacts smoothly with the (deprotonated) nucleophile (see Fig. 4).

When activation by DABCO is used in the case of compounds of type **12**, which contain both a ketene and a hydroxy group at a suitable distance from each other, macrocyclic mono- or di-(and tri-)lactones are formed (Scheme 1).



Scheme 1.



Scheme 2.

Scheme 2 outlines how *rac*-**13a** or *rac*-**13b** is accessible lastly from **16a** and the corresponding ω-bromoalkanols.

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[3] G. Fischer, Dissertation, Universität Frankfurt am Main 1983.

[4] **14**: M.p. = 124–125°C (CH_2Cl_2/*n*-pentane); UV (CH_3OH): $\lambda_{max}(\varepsilon)$ = 235 nm (41366); IR (KBr): 1755 (enol acetate), 1735 (lactone), 1210 (C–O) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ = 1.48–1.70 (m, 8H, 9,10,20,21-H), 2.16 (s, 6H, $COCH_3$), 2.37 (t, J = 7.6 Hz, 4H, 8,19-H), 3.14 (dd, J_{vic} = 7.8 Hz, J_{allyl} = 1.4 Hz, 4H, 3,14-H), 4.13 (t, J = 6.1 Hz, 4H, 11,22-H), 5.59–5.63 (m, 2H, 4,15-H), 6.02 (d, J_{vic} = 11.9 Hz, 2H, 6,17-H), 6.11–6.21 (m, 2H, 5,16-H); ^{13}C-NMR ($CDCl_3$): δ = 20.95 (q, CH_3), 23.51, 27.58, 29.18 (each t, 8,9,10,19,20,21-C), 34.22 (t, 3,14-C), 64.00 (t, 11,22-C), 113.46, 122.78, 124.28 (each d, 4,5,6,15,16,17-C), 152.55 (s, 7,18-C), 169.22 (s, C=O-acetate), 170.88 (s, 2,13-C); MS: m/z = 448 (M^+); M_r: 438 (vap. press. osm.), calc. 448.5.

[5] U.-M. Billhardt, planned Dissertation.

[6] *rac*-**13a**: M.p. = 73–74°C (pentane); UV (CH_3OH): $\lambda_{max}(\varepsilon)$ = 242 nm (21970); IR (KBr): 1752 (enol acetate), 1735 cm^{-1} (lactone); ^{1}H-NMR ($CDCl_3$): δ = 1.09–1.66 (m, 14H, 9- to 15-H), 1.23 (d, J = 6.8 Hz, 3H, 3-CH_3), 2.17 (s, 3H, $COCH_3$), 2.35, 2.65 (each m, 2H, 8-H), 3.49 (m, 1H, 3-H), 3.99, 4.20 (each m, 2H, 16-H), 5.32 (m, 1H, 4-H), 6.20 (m, 2H, 5,6-H); ^{13}C-NMR ($CDCl_3$): δ = 16.42 (q, 3-CH_3), 20.99 (q, CH_3-acetate), 24.76, 25.23, 25.76, 26.03, 26.71, 27.12, 28.20, 28.79 (each t, 8- bis 15-C), 38.59 (d, 3-C), 64.94 (t, 16-C), 114.91, 123.79, 130.94 (each d, 4- to 6-C), 152.21 (s, 7-C), 169.42 (s, C=O-acetate), 174.25 (s, 2-C); MS: m/z = 308 (M^+); M_r: 302 (vap. press. osm.), calc. 308.4.

[7] *rac*-**13b**: M.p. = 43–44°C (pentane); UV (CH_3OH): $\lambda_{max}(\varepsilon)$ = 241 nm (23493); IR (KBr): 1755, 1730 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ = 1.11–1.62 (m, 18H, 9- to 17-H), 1.23 (d, J = 6.9 Hz, 3H, 3-CH_3), 2.16 (s, 3H, $COCH_3$), 2.29, 2.61 (each m, 2H, 8-H), 3.49 (m, 1H, 3-H), 4.04, 4.19 (each m, 2H, 18-H), 5.40 (m, 1H, 4-H), 6.15 (m, 2H, 5-, 6-H); ^{13}C-NMR ($CDCl_3$): δ = 17.29 (q, 3-CH_3), 21.01 (q, CH_3-acetate), 24.42, 25.48, 26.35, 26.57, 27.55, 27.80, 27.95, 28.20, 28.46 (each t, 8- to 17-C), 38.78 (d, 3-C), 64.41 (t, 18-C), 114.57, 123.16, 130.57 (each d, 4- to 6-C), 152.36 (s, 7-C), 169.45 (s, C=O-acetate), 174.50 (s, 2-C); MS: m/z = 336 (M^+); M_r: 335 (vap. press. osm.), calc. 336.46.

[8] **14**: a = 8.383(2), b = 9.096(3), c = 9.489(1) Å, α = 111.53(1), β = 111.85(2), γ = 93.44(3)°; V = 608.3 Å^3; triclinic, P$\bar{1}$, Z = 1; $C_{24}H_{32}O_8$; ρ_{calc} = 1.225 g/cm^3, 22°C; Enraf-Nonius CAD4 diffractometer; $Mo_{K\alpha}$ radiation; sphere up to 2ϑ = 47°; 1731 independent reflections with $I > 0.2\sigma$; $R(F)$ = 0.048; R_w = 0.052; SDP system of programs.

[9] Further details of the crystal structure investigations are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD 50829, the names of the authors, and the journal citation.

[10] *rac*-**13a**: a = 5.412(1), b = 17.300(4), c = 18.693(2) Å; β = 92.02(1)°; V = 1749.1 Å^3 (−100°C); monoclinic; $P2_1/n$; Z = 4; $C_{18}H_{28}O_4$; ρ_{calc} = 1.171 (−100°C), ρ_{exp} = 1.14 (20°C) g/cm^3; R3 diffractometer (Nicolet); $2\vartheta/\vartheta$ scan; $Mo_{K\alpha}$; −100°C; 3163 [$F > \sigma(F)$] of 4230 independent reflections (ϑ_{max} = 28°); R_w = 0.051 [$W = 1/\sigma^2(F)$]; G. M. Sheldrick: *SHELXTL, An Integrated System for Solving, Refining and Displaying Crystal Structures from Diffraction Data,* Universität Göttingen 1983.

Adducts of the Ketene (1*E*,3*Z*)-1,2,3,4,5-Pentamethyl-6-oxo-1,3,5-hexatrienyl Acetate

By *Gerhard Quinkert*, Uta-Maria Billhardt, Erich F. Paulus, Jan W. Bats,* and *Hartmut Fuess*

The structures of some adducts of dienyl ketenes and protic nucleophiles have been determined unambiguously: by chemical conversion into known compounds[1], by directed synthesis[2], or by X-ray structure analysis[3]. In most cases, however, the structures have been deduced from the various spectroscopic data characteristic for certain partial structures. Such spectroscopic assignments are to be used with care if the linear adduct is highly branched: for instance, in the case of adducts of the title compound,

$$O{=}C{=}CMe{-}CMe\overset{Z}{=}CMe{-}CMe\overset{E}{=}CMe{-}O{-}COCH_3$$

which is kinetically unstable under normal conditions.

After irradiation of cyclohexylamine-containing ether solutions of *rac*-**1**[4] with UV light (> 340 nm) the two crystalline adducts *rac*-**2b**[5] and *rac*-**3**[6,7] can be isolated. In neither case can it even be established from the data obtained by conventional spectroscopic methods whether the isomer is a 1,2-, 1,4-, or 1,6-adduct. According to the NMR spectra, *rac*-**2b** consists of two rotamers in solution[8]. From the products of ozonolysis[9] it must have been formed by 1,2-addition to the title compound. The single-crystal structure analysis[10,11] confirms this and, moreover, establishes the orientation of the ligands at the CC double bonds (see Fig. 1).

A comparison of the crystal structures of *rac*-**4**[11,12] (see Fig. 2) and *rac*-**2b** reveals the influence of the methyl

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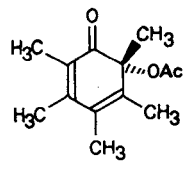

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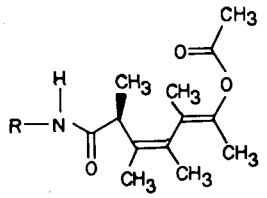
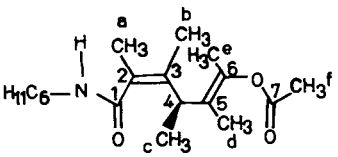


2a: R = H
2b: R = C_6H_{11}



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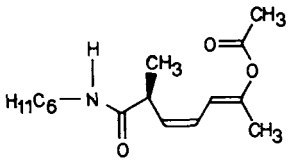

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groups on the conformations: An intramolecular H-bridge between the amide nitrogen and the ester carbonyl oxygen explains the anomalous properties[13] of *rac*-**2b** compared to *rac*-**4**[1a].

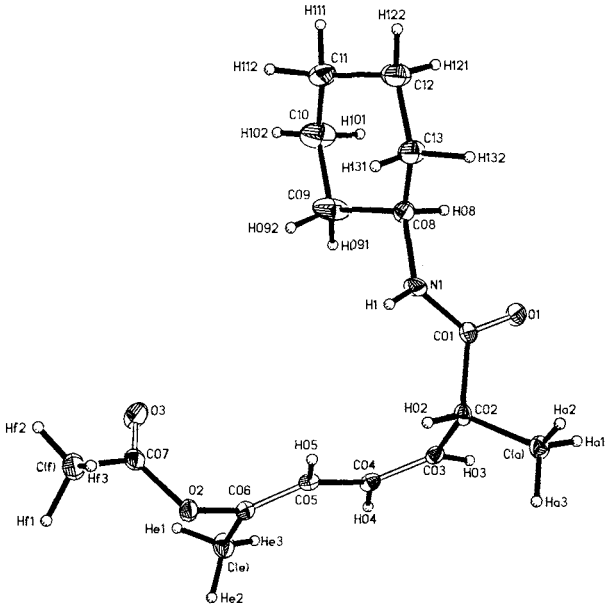

Fig. 2. Structure of *rac*-4 in the crystal [11, 12].

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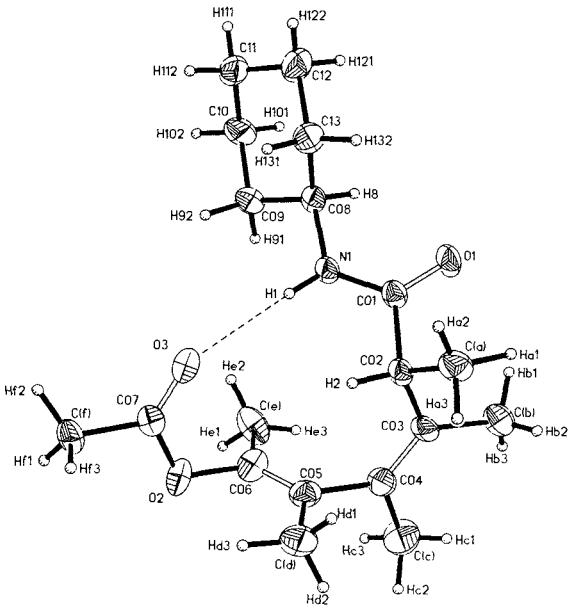


Fig. 1. Structure of *rac*-**2b** in the crystal [10, 11].

rac-**3** has been recognized[15] as a 1,4-adduct by a new two-dimensional NMR technique for the determination of connectivity[14]. All the signals of the C-atoms 1 to 7 and of the protons of the methyl groups a to f are assigned by this method. Measurements at 500 MHz have provided evidence of nuclear Overhauser effects (NOE) only between a and b (2.5% in both directions) or the methine proton on C-4 and e (from e: 4%): hence, it follows that *rac*-**3** has the 2*Z*,5*E* configuration. The 3*Z*,5*E*-configuration of *rac*-**2b** and the 2*Z*,5*E* configuration of *rac*-**3** are consistent with the view how these adducts are formed from the title compound[16].

[1] a) D. H. R. Barton, G. Quinkert, *J. Chem. Soc. 1960*, 1; b) G. Quinkert, B. Bronstert, D. Egert, P. Michaelis, P. Jürges, G. Prescher, A. Syldatk, H.-H. Perkampus, *Chem. Ber. 109* (1976) 1332.
[2] G. Quinkert, M. Hintzmann, P. Michaelis, P. Jürges, H. Appelt, U. Krüger, *Justus Liebigs Ann. Chem. 748* (1971) 38.
[3] W. Dannenberg, H. Perst, W. J. Seifert, *Tetrahedron Lett. 1975*, 3481.
[4] A. J. Waring, M. R. Morris, M. M. Islam, *J. Chem. Soc. C 1971*, 3274.
[5] *rac*-**2b**: M.p. 75—76°C (ether/pentane); UV (CH_3OH): no absorption >220 nm; IR (KBr): 3365 (amide-NH), 1730 (enol acetate), 1665 cm^{-1} (amide-CO); ^{1}H-NMR (C_6D_6): δ=1.33, 1.37 (2d, J=7.0 Hz, 3H, 2-CH_3), 1.50 (d, J=1.5 Hz, 3H, 5-CH_3), 1.59, 1.60 (2d, J=1.0 Hz, 3H, 4-CH_3), 1.66, 1.69 (2s, 3H, $COCH_3$), 1.75 (d, J=1.5 Hz, 3H, 6-CH_3), 1.88, 1.95 (2d, J=1.0 Hz, 3H, 3-CH_3), 1.00—2.10 (m, 10H, cyclohexyl-CH_2), 3.38, 3.82 (2q, J=7.0 Hz, 1H, 2-H), 4.02 (m, 1H, cyclohexyl-CH), 6.08, 6.62 (2m, 1H, NH); the signal doubling corresponds to a rotameric ratio of ca. 3:1. ^{13}C-NMR (CD_2Cl_2): δ=11.79, 12.69, 14.02, 14.57, 15.60, 15.96, 16.35, 16.39, 16.68 (each q, CH_3), 19.80, 19.89 (2q, acetate methyl-C), 24.34, 24.70, 24.72, 24.92, 25.15, 32.35, 32.43, 32.49, 32.66 (each t, cyclohexyl methylene-C), 42.90, 43.89, 46.98, 47.47 (each d, 2-C, cyclohexyl methine-C), 124.80, 126.22 (2s, 5-C), 128.60, 129.65 (2s, 4-C), 131.13, 131.76 (2s, 3-C), 139.37, 139.66 (2s, 6-C), 168.81, 169.69 (2s, acetate carbonyl-C), 171.63, 171.97 (2s, amide carbonyl-C).
[6] *rac*-**3**: M.p.=141—142°C (ether/pentane); UV (CH_3OH): no absorption >220 nm; IR (KBr): 3250 (amide-NH), 1758 (enol acetate), 1616 cm^{-1} (amide carbonyl); ^{1}H-NMR (C_6D_6): δ=1.10 (d, J=7.2 Hz, 3H, 4-CH_3), 1.55 (d, J=1.0 Hz, 3H, 3-CH_3), 1.61 (d, J=1.4 Hz, 3H, 5-CH_3), 1.69 (d, J=1.0 Hz, 3H, 2-CH_3), 1.70 (s, 3H, CO—CH_3), 2.06 (d, J=1.4 Hz, 3H, 6-CH_3), 0.88—1.88 (m, 10H, cyclohexyl-CH_2), 3.94 (m, 2H, 4-H and cyclohexyl-CH), 4.88 (m, 1H, NH); ^{13}C-NMR ($CDCl_3$): δ=13.56, 14.63, 17.03, 17.41, 18.44 (each q, CH_3), 21.45 (q, acetate methyl-C), 25.68, 26.27, 33.62, 33.81 (each t, cyclohexyl methylene-C), 39.12, 48.97 (each d, 4-C and cyclohexyl methine-C), 124.99 (s, 5-C), 128.41 (s, 2-C), 138.10 (s, 3-C), 142.18 (s, 6-C), 169.64 (s, acetate carbonyl-C), 172.18 (s, amide carbonyl-C).
[7] In an earlier work only one adduct was isolated, which, correctly, was regarded as a 1,2-adduct; see [4].
[8] Since this is also the case in *rac*-**2a**, the torsional isomerism established here is caused by an increased barrier to rotation about the C-4/C-5 bond and not about the C—N bond of the amide. The rotamer dominant under normal conditions corresponds, according to the low-temperature NMR spectrum (see [14]), to the conformation prevalent in the crystal.
[9] Biacetyl (converted into 2,3-dimethylquinoxaline) and (*R*,*S*)-2-methyl-3-oxobutyric acid *N*-cyclohexylamide.
[10] *rac*-**2b**: a=11.7429(7), b=12.708(1), c=13.244(2) Å, β=91.44(1)°; V=1975.7(7) Å^3; monoclinic; $P2_1/c$, Z=4; $C_{19}H_{31}NO_3$; ρ_{calc}=1.081 g/cm^3; Enraf-Nonius CAD4 diffractometer; $Mo_{K\alpha}$; 22°C; hemisphere up to 2ϑ=44°; 2192 independent reflections with $I>10.3\sigma$; R=0.070; R_w=0.050; SDP program system.

[11] Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD 50864, the names of the authors, and the journal citation.
[12] *rac*-4: $a=18.397(3)$, $b=18.397(3)$, $c=9.712(2)$ Å; $V=3287.0$ Å^3 (-100 °C); tetragonal, $P\bar{4}2_1c$; $Z=8$; $C_{16}H_{25}NO_3$; $\rho_{calc}=1.129$ (-100 °C), $\rho_{exp}=1.10$ (20 °C) g/cm^3; R3 diffractometer (Nicolet); $2\vartheta/\vartheta$ scan; $Mo_{K\alpha}$, -100 °C; 2058 [$F>\sigma(F)$] from 2246 independent reflections ($\vartheta_{max}=28°$), $R_w=0.038$ [$w=1/\sigma^2(F)$]; G. M. Sheldrick: SHELXTL, An Integrated System for Solving, Refining and Displaying Crystal Structures from Diffraction Data, Universität Göttingen, 1983.
[13] Extremely good solubility in and readily eluted from silica gel by apolar solvents; bathochromic shift of the IR absorption bands for the enol acetate group.
[14] H. Kessler, C. Griesinger, J. Lautz, *Angew. Chem. 96* (1984) 434; *Angew. Chem. Int. Ed. Engl. 23* (1984) 444.
[15] Confirmed by the *N*-cyclohexylamide of the pyruvic acid formed on ozonolysis and by ready conversion under mild transesterification conditions of the enol acetate *rac*-3 into the two diastereomeric racemic mixtures of the respective ketones.
[16] G. Quinkert in W. Bartmann, E. Winterfeldt: *Stereoselective Synthesis of Natural Products, Workshop Conferences Hoechst, Vol. 7*, Excerpta Medica, Amsterdam 1979, p. 151, and literature cited therein.

Determination of Connectivities via Small Proton-Carbon Couplings with a New Two-Dimensional NMR Technique**

By *Horst Kessler**, *Christian Griesinger*, and *Jörg Lautz*

The scalar spin-spin couplings observable in NMR spectra are brought about by bonding and thus provide information about atomic linkages. Hitherto, only carbon-carbon (INADEQUATE)[1] or proton-proton couplings (H,H-COSY)[2] have been used for establishing the connectivity of carbon atoms in organic compounds (Fig. 1). If

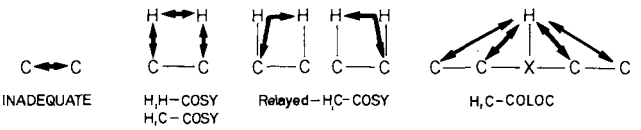


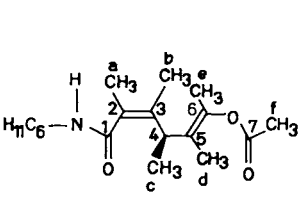
Fig. 1. NMR spectroscopic methods for locating carbon linkages.

proton couplings are used, this information is obtained in an indirect way via an additional H,C-COSY spectrum[3]. If relevant signals overlap, the relayed H,C-COSY technique[4] often enables an unequivocal assignment. Herein we describe the use of two-dimensional heteronuclear shift correlation via small couplings (H,C-COLOC = *CO*rrelation spectroscopy via *LO*ng range *C*ouplings). The conventional H,C-COSY pulse sequence[3] has the disadvantage that the intensity of the cross peaks not only depends on $^2J_{CH}$ and $^3J_{CH}$ couplings of differing sizes but also on couplings between the protons themselves and the direct CH coupling ($^1J_{CH}$). An optimization of the parameters prior to carrying out the two-dimensional experiment is not possible in the conventional sequence. We therefore propose the following pulse sequence H,C-COLOC[5], in which the evolution time (t_1) is incorporated in the time in which H,C-couplings develop (Δ_1):

$$\begin{array}{lllll} ^1H & (\pi/2)_{\phi_1}, t_1/2, & (\pi)_{\phi_2}, & (\Delta_1 - t_1/2), & (\pi/2)_{\phi_3}, \Delta_2, BB \\ ^{13}C & & (\pi)_{\phi_4}, & & (\pi/2)_{\phi_5}, \quad AQ_{\phi_{det}} \end{array}$$

Compared to conventional H,C-COSY, the H,C-COLOC sequence has the advantage of an easy optimization of the Δ_1 and Δ_2 delays for development of small couplings by INEPT measurements[6]. Because of the constant length of the pulse sequence, the parameters so determined are also valid for the whole 2D experiment. In addition, an improved signal-to-noise ratio results from the pulse sequence shortened by t_1 and the homonuclear broad-band decoupling in t_1[5].

The following two examples demonstrate the application of the new technique. On irradiation of *rac*-(1,2,3,4,5-pentamethyl-6-oxo-2,4-cyclohexadienyl) acetate (*rac*-6-acetoxy-2,3,4,5,6-pentamethyl-2,4-cyclohexadien-1-one) in the presence of cyclohexylamine as protic nucleophile, the two adducts *rac*-**1**[7] and *rac*-**2**[7,8] are formed. An NMR-spectroscopic characterization of the two isomers by 2D-INADEQUATE is not very attractive because of the large



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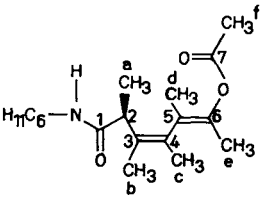

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amounts of substance necessary for the measurement and the large spectral range of the ^{13}C-NMR signals (ca. 150 ppm) with various $^1J_{CC}$ coupling constants. Techniques which are designed for the measurement of carbons directly bonded to protons cannot be used because of the missing protons at the olefinic carbons. In the COLOC spectrum of *rac*-**1**, elucidation of the constitution via determination of the connectivities is possible (Fig. 2): Cross peaks are visible for all cases where the carbon atoms couple with protons via several bonds.

It is convenient to start the interpretation of the spectrum with the downfield carbonyl signals. Signal 7 shows only one cross peak with the signal of the protons of the methyl group f. The latter do not couple with any other olefinic C-atom; f can thus be assigned to the acetyl moiety. The carbonyl carbon 1 couples with the protons of the methyl group a, which, in turn, exhibit couplings with the olefinic C-atoms 3 and 2. Of these, only C3 couples with the protons of the methyl group c, which are easily identified as a doublet in the ^{1}H-NMR spectrum. C5 also couples with c. The signals 5 and 6 form cross peaks with d and e. It follows from the cross-sections through C5 and C6 (not shown here) that the cross peaks of C5 with d and of C6 with e are the most intense. C,H couplings via two and three bonds are, of course, of the same order of magnitude; however, it is seen from the higher intensity of 2-a and 3-b compared to 2-b and 3-a that in the case of the parameters chosen here, the geminal coupling is more developed than the vicinal coupling. The protons of the methyl groups d and e can also be assigned under these assumptions. The experiment thus enables the sequencing and assignment of the signals of all the olefinic carbon atoms and methyl protons. Hence, all the requirements for determining the configuration at the two double bonds by NOE difference spectroscopy are fulfilled[7]. Noteworthy is the sharpness of the cross peaks 3-c and 5-c, which results from homonuclear proton decoupling.

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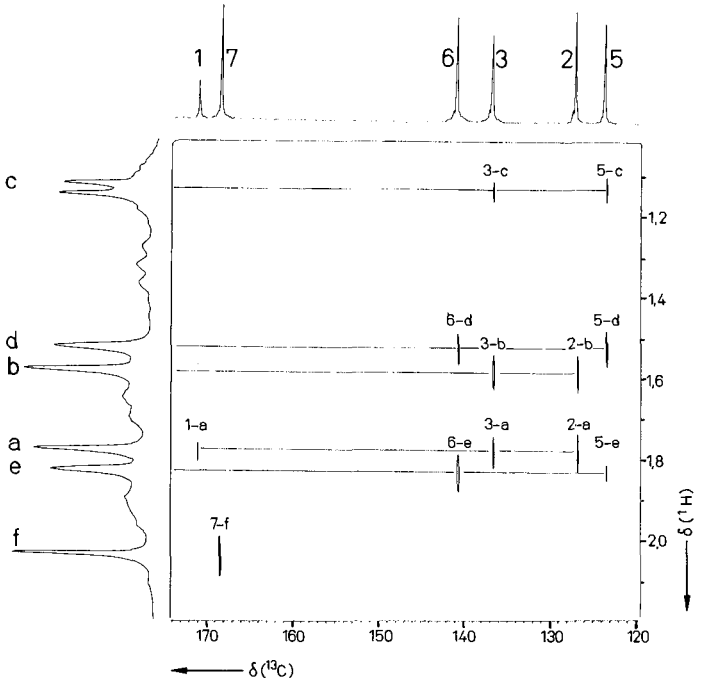

Fig. 2. Section of the H,C-COLOC spectrum of *rac*-**1** for the olefinic carbon atoms and the carbonyl groups, in the proton region of the methyl groups. Spectrometer: Bruker WH 270. Measuring conditions: 150 mg in 2 mL $CDCl_3/C_6D_6$ (5:1); $\Delta_1=\Delta_2=40$ ms; spectral width in $\omega_1=1850$ Hz, in $\omega_2=3625$ Hz. Total duration of a scan 1.5 s. 140 increments of 1 K with 192 scans each. Total recording time: 12 h. The phases of the 90°-^{1}H-pulse were cycled independently of one another in 90° steps with respect to the receiver phase ($\phi_1=k\times90°$, $\phi_{det}=-k\times90°$, $k=0, 1, 2, \ldots$ and $\phi_3=m\times90°$, $\phi_{det}=-m\times90°$, $m=0, 1, 2, \ldots$; $\phi_2=\phi_4=\phi_5=0$).

The spectrum of *rac*-**2** (Fig. 3) reveals the presence of two conformers in solution, of which the dominating one has the conformation determined in the crystal. This was proven by dissolution at −80 °C in CD_2Cl_2 and immediate ^{1}H-NMR measurements[9]. The conformation occurring on warming the solution is formed through steric hindrance of rotation about the single bond between C4 and C5[7]. The H,C-COLOC spectrum of the dominating conformation can be interpreted completely analogously to that of the isomeric *rac*-**1**.

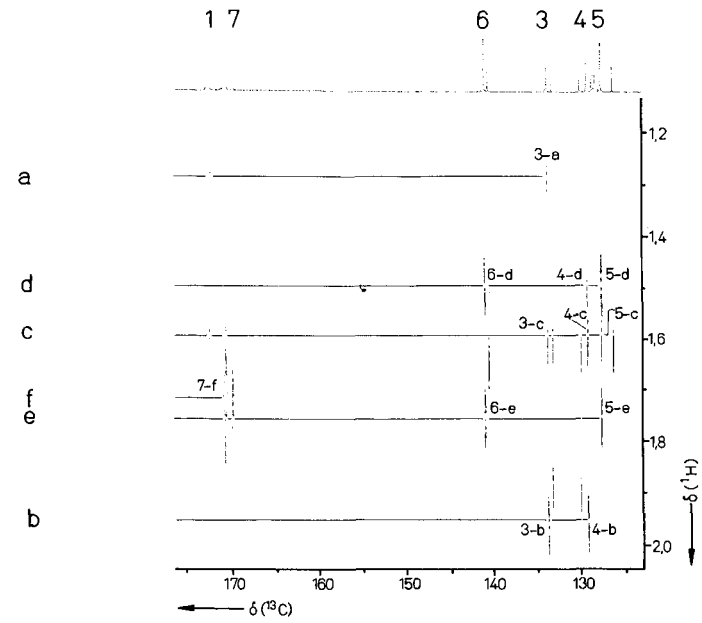

Fig. 3. Section of the H,C-COLOC spectrum of *rac*-**2**. Spectrometer: Bruker AM 500. Measuring conditions: 240 mg in 2 mL C_6D_6. $\Delta_1=60$ ms, $\Delta_2=40$ ms; spectral width in $\omega_1=3800$ Hz, in $\omega_2=6670$ Hz. Total duration per scan 1.5 s. 180 increments of 4 K with 128 scans each. Total recording time: 10 h. Other than for the spectrum in Figure 2, the phase of the 90°-^{13}C-pulse was also cycled with respect to the receiver phase ($\phi_5=n\times90°$, $\phi_{det}=n\times90°$, $n=0, 1, 2, \ldots$; $\phi_2=\phi_4=0$). This led to a better suppression of spectral artefacts.

The method presented here, which employs H,C-couplings via two and three bonds, can be used with advantage for the assignment of quaternary carbon atoms, whose environment is thus also determinable. For its application to aliphatic carbon atoms we recommend the use of a low-pass J filter[10] for suppressing the direct C–H cross signals[11]. The new pulse sequence enables a convenient and, other than the conventional H,C-COSY sequence, effective optimization of the delay for the whole experiment. It is especially suitable, therefore, for the investigation of complex molecules, where intensity maximization is of importance due to scarcity of substance or short relaxation times.

The sensitivity of the experiment described here, like that in the relayed H,C-COSY technique, can be rated between that of H,C-COSY and 2D-INADEQUATE.

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Pigments from the Cap Cuticle of the Bay Boletus *(Xerocomus badius)***

By *Bert Steffan* and *Wolfgang Steglich**

Dedicated to Professor Sir Derek Barton on the occasion of his 65th birthday

The bay boletus [*Xerocomus badius* (Fr.) Kühn. ex Gilb.], highly prized as an edible fungus, has a chocolate-brown pileus. The pigments contained therein are apparently present in the form of salts, since addition of a small amount of hydrochloric acid is necessary for their extrac-

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tion with methanol-acetone. The separation and purification of the pigments can be achieved by multiple chromatography on Sephadex LH20 with methanol as eluent; besides the main products badion A **2a** and norbadion A **4a**, bisnorbadioquinone A **5a** and *O*-methylpulviquinone A **6b** are also obtained. The pigments can be easily recognized on TLC plates by their color reaction with ammonia vapor (Table 1).

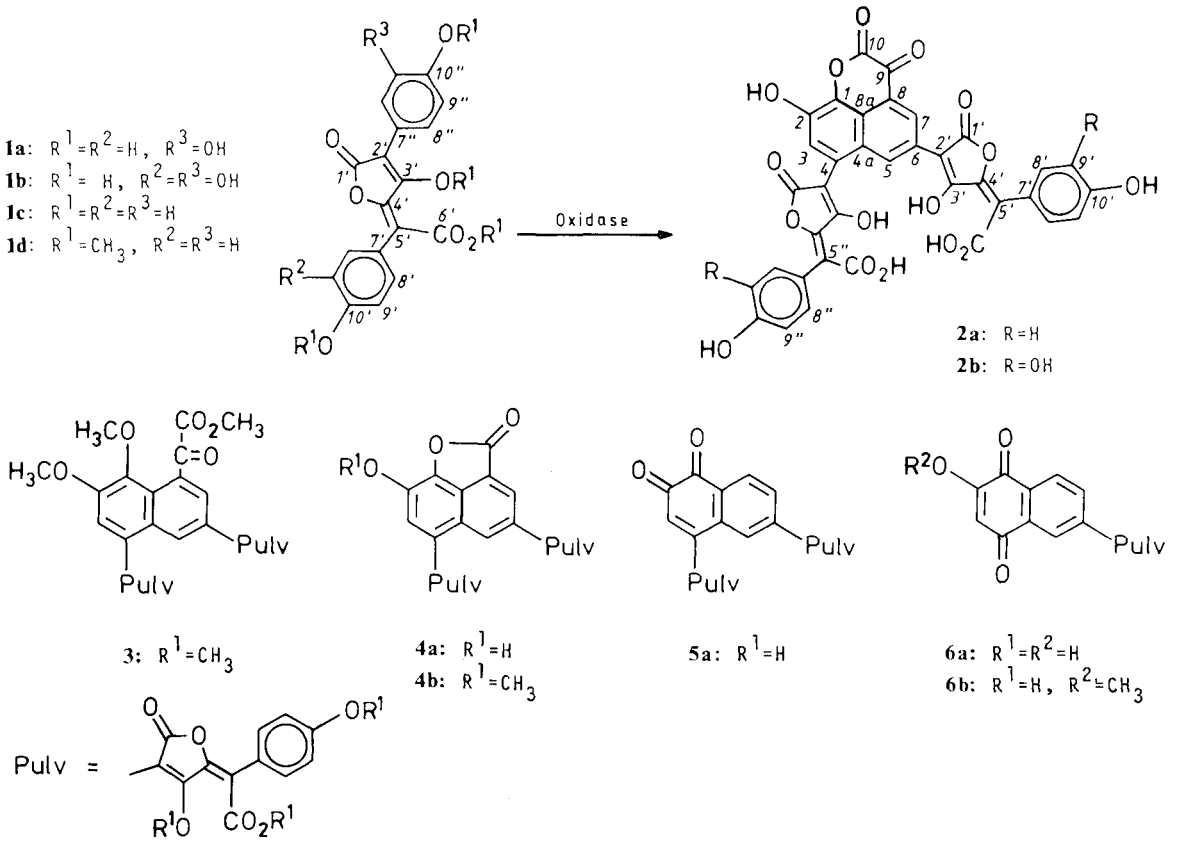

Table 1. Thin-layer chromatographic characterization of the cap cuticle pigments.

Pigment	R_F [a]	Color	Color over NH_3	Rel. amount [b]
2a	0.83 (I)	brown	green	100
4a	0.89 (I)	yellow-brown	salmon color	30
5a	0.83 (I)	brown	violet	10
6b	0.24 (II)	yellow-brown	red-violet	2

[a] I: TLC-Al foil aluminum oxide 150 F_{254} Merck, impregnated with saturated ethanolic ascorbic acid solution (eluent: 2-butanone/formic acid/water = 15 : 3 : 2); II: TLC-Al foil silica gel 60 F_{254} Merck (eluent: benzene/ethyl formate/formic acid = 10 : 5 : 3). [b] Referred to **2a** = 100.

Badion A **2a** forms blackish brown, shiny microcrystals, which decompose without defined melting point above 250°C and do not furnish any molecular ions with the usual MS techniques (EI, FD, FAB). According to elemental analyses and the X-ray emission spectra both **2a** as well as **4a** contain potassium, which can be removed only with difficulty, even by washing with dilute hydrochloric acid. The reddish brown solution of **2a** in methanol shows absorption maxima at $\lambda_{max} = 260$, 368, and 482 nm (sh). The ^{1}H-NMR spectrum ([D]$_6$DMSO) shows a singlet at $\delta = 7.31$ (1H) and two 1.5 Hz doublets at unusually low field ($\delta = 9.06$ and 9.26, 2H) besides the signals for two *p*-hydroxyphenyl moieties. Methylation with dimethyl sulfate/potassium carbonate in acetone affords a lemon-yellow nonamethyl derivative **3**, m.p. 255—257°C, which, according to high resolution MS, has the empirical formula $C_{45}H_{38}O_{17}$.

This indicates **2a** as having a C_{36} skeleton, and thus a biogenesis by oxidative dimerization of xerocomic acid **1a** ($C_{18}H_{12}O_7$). **1a** has already been isolated from the bay boletus[1] and recognized as a component responsible for the blue coloration of the flesh on being damaged[2]. Indeed, it is found on comparing the coupled ^{13}C-NMR spectra of **2a** and **3** with those of atromentic acid **1c** and its permethyl derivative **1d** that **2a** contains two pulvinic acid substructures (Table 2). Systematic selective decouplings, paying special attention to long-distance coupling, shows that the two pulvinic acid moieties in **3** are located at the 4,6-positions of a naphthalene nucleus bearing two methoxy groups in the 1,2-position and a CH_3O_2C—CO moiety at the 8-position.

Since the low-temperature ^{1}H-NMR spectrum ([D$_6$]acetone, 170 K) of **2a** shows only signals for three protons at $\delta = 9.51$, 9.63, and 10.70 in the region characteristic for phenolic OH groups, i.e. between $\delta = 9.5-11$, it must be present as naphtho[1,8-*bc*]pyrandione[4]. Hence, the methylation of **2a** to **3** proceeds via opening of the lactone ring. The structure **2a** fully explains the downfield position of the NMR signals of H-5 and H-7, since these protons are exposed to the deshielding effect of both the 9-carbonyl group as well as that of the pulvinic acid moiety on C-6[5].

Methylation of norbadion A **4a** furnishes a heptamethyl derivative $C_{42}H_{32}O_{15}$ **4b**, m.p. 247—249°C. The ^{1}H-NMR spectrum of **4a** is almost the same as that of **2a**[6], and, according to the ^{13}C-NMR data, it contains a dihydroxy-

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Table 2. ^{13}C-NMR data of **2a**, **3**, **1c**, and **1d** (100.62 MHz, δ-values, solvent as internal standard).

	2a ([D$_6$]DMSO]	**3** ($CDCl_3$)		**2a** ([D$_6$]DMSO)	**3** ($CDCl_3$)	**1c** (CD_3OD)	**1d** ($CDCl_3$)
C-1	130.60 d 7.1	142.41 dq 6.8/3.8	C-1′/1″	168.50 s	167.40 s	168.7 s	168.1 s
C-2	142.57 d 2.3	148.87 dq 2.1/3.8		168.51 s	168.00 s		
C-3	121.86 D 162	119.55 D 160	C-2′/2″	95.30 d 4.8	102.70 d 5	105.0 t 4.3	108.2 t 4.3
C-4	127.96 dd 5/1.5	123.80 dd 4.8/1.9		93.44 dd 4.3/4.0	106.20 t 4.8		
C-4a	125.67 dd 8.6/1.2	128.01 dd 8/1.2	C-3′/3″	166.72 s	163.65 q 3.8	160.8 s	162.2 s
C-5	131.16 Dd 165/6.5	129.66 Dd 162/6		166.92 s	164.45 q 3.8		
C-6	128.92* br. s	133.92 br. s	C-4′/4″	151.54 s	139.42 s	154.6 s	140.3 s
C-7	126.09 Dd 165/7.4	128.23 Dd 164/7.3		151.89 s	139.79 s		
C-8	125.29* br. s	125.01 br. s	C-5′/5″	117.89 t 3.9	117.09 t 4.2	118.3 t 4.0	115.6 t 4.2
C-8a	119.94 dd 6.8/7.3	126.74 dd 6.7/6.6		117.93 t 3.9	117.69 t 4.2		
C-9	173.03 d 4.5	187.30 d 4.8	C-6′/6″	171.38 s	166.87 q 3.8	174.8 s	167.4 q 4
C-10	154.75 s	161.19 q 3.8		172.23 s	166.96 q 3.8		
			C-7′/7″	126.16 t 8	123.29 t 8	125.6 t 8.2	123.6 t 8
				126.33 t 8	123.43 t 8	122.1 t 8.2	120.6 t 8
			C-8′/8″**	131.44 Dd 162/7.2	130.88 Dd 161/7.3	130.3 Dd 160/7.2	130.8 Dd 161/7
				131.46 Dd 162/7.2	130.93 Dd 161/7.3	132.7 Dd 150/7.2	131.0 Dd 161/7
			C-9′/9″**	114.02 Dd 159/4.8	114.32 Dd 161/5	115.6 Dd 160/4.6	114.0 Dd 160/5
				114.16 Dd 159/4.8	114.35 Dd 161/5	116.2 Dd 160/4.6	114.3 Dd 160/5
			C-10′/10″	156.47 tt 9/2.7	160.57 m	158.6 m	160.1 m
				156.59 tt 9/2.7	160.69 m	158.7 m	160.5 m

3: 1-OCH_3 (60.5, Q, J=146.4 Hz), 2-OCH_3 (56.7, 145.0), 10-OCH_3 (52.9, 148.1), 3′/3″-OCH_3 (60.8/61.8, 148.4/148.4), 6′/6″-OCH_3 (52.7/52.8, 147.6/147.6), 10′/10″-OCH_3 (55.32/55.33, 144.2/144.2); **1d**: 3′-OCH_3 (60.9, Q, J=147.7 Hz), 6′-OCH_3 (52.7, 147.7), 10′/10″-OCH_3 (55.3, 144.6)

[*] Assignment may be reversed. [**] Signals for double the number of C atoms.

naphthalene moiety with two pulvinic acid side chains. The side chain at the 8-position, however, is one carbon atom shorter than the other, and forms a γ-lactone with the 1-OH group (^{13}C-NMR: δ(9-CO)=167.12, d, J=3.5 Hz, in [D$_6$]DMSO).

Apparently, the component **2a** of the fungus is capable of further degradation; in bisnorbadioquinone A **5a**[6] the side chain at the 8-position is missing, and the hydroxy groups are oxidized.

Formation of pulviquinone A **6a** from **5a** by oxidative elimination of the pulvinic acid chain at the 4-position is conceivable. The brownish red pigment is isolated as the methyl ether **6b**, which is most likely formed during the extraction with acidified methanol. In order to demonstrate the role of xerocomic acid **1a** as a biogenetic precursor of badion A **2a**, a portion of the cap cuticle was removed from a bay boletus and the underlying white flesh treated with aqueous xerocomic acid solution. The resulting yellow spot became bluish green within a few minutes and gradually turned brown in color. After extraction and chromatographic separation of the resulting pigment, **2a** could be detected ^{1}H-NMR spectroscopically. Thus, the enzymes necessary for the oxidative dimerization of **1a** appear to be fixed to the cap cuticle. Badion A **2a** is also the pigment of *Boletus pinicola* Vitt., a close relative of the cep. Interestingly, in *Boletus erythropus* (Fr. ex Fr.) Pers. it is replaced by badion B **2b**, which is biogenetically derived from variegatic acid **1b**[7].

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1c, 90320-59-5; **1d**, 90295-65-1; **2a**, 90295-66-2; **3**, 90295-67-3; **4a**, 90295-68-4; **4b**, 90295-69-5; **5a**, 90295-70-8; **6b**, 90295-71-9.

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[4] A yellow pigment containing a naphtho[1,8-*bc*]pyrandione system has also been isolated from the culture filtrate of the phytopathogenic fungus *Gremmeniella abietina*: W. A. Ayer, Y. Hoyano, I. Altena, Y. Hiratsuka, *Rev. Latinoam. Quim. 1982*, 84.
[5] W. Steglich, H. Besl, K. Zipfel, *Z. Naturforsch. B 29* (1974) 96.
[6] UV (MeOH). **4a**: λ_{max}=260, 367, 406 nm (sh); **4a**: 250 (sh), 307, 356, 415 nm (sh); **6a**: 265 (sh), 278, 312, 354, 422 nm.—^{1}H-NMR ([D$_6$]DMSO). **4a**: δ=6.76, 6.79, 7.09, 7.12 (each d, J=8.9 Hz, 8H), 7.39 (s, 1H), 9.04, 9.44 (each d, J=0.9 Hz, 2H); **5a**: 6.45 (s, 1H), 6.73, 6.75, 7.05, 7.08 (each d, J=8.5 Hz, 8H), 7.89 (d, J=8.2 Hz, 1H), 8.33 (dd, J=8.2 and 1.5 Hz, 1H), 8.53 (d, J=1.5 Hz, 1H), 9.46, 9.50, 17.56, 17.83 (each br. s, 4OH); **6b**: 3.83 (s, 3H), 6.28 (s, 1H), 6.73, 7.07 (each d, J=8.5 Hz, 4H), 7.93 (d, J=8.3 Hz, 1H), 8.56 (dd, J=8.3 and 1.6 Hz, 1H), 8.82 (d, J=1.6 Hz, 1H).
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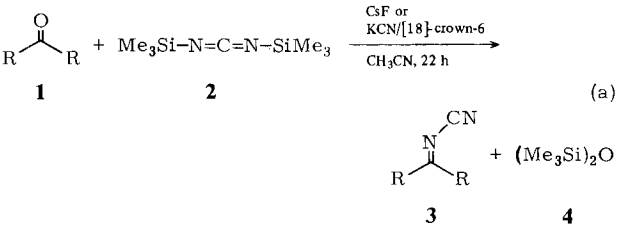
One-Step Entry to *N*-Cyanimines and to *N,N′*-Dicyanoquinonediimines, a Novel Class of Electron-Acceptors**

By *Alexander Aumüller* and *Siegfried Hünig**

N-Cyanimines **3** are accessible from alkenes and cyanazide[1], as well as from certain carbodiimides and isothiocyanates[2]. Hitherto all reactions in which ketones have been used as starting substances have involved several steps[3]. Herein we describe the one-step conversion $>C=O \rightarrow >C=N-CN$, which can be applied to (non-enolizing) ketones and to *p*-quinones. The crucial reagent is bis(trimethylsilyl)carbodiimide **2**[4], which converts, e.g., benzophenone (62—70%)[5] and fluorenone (75%)[5] into **3** in the presence of fluoride or cyanide catalysts according to equation (a).



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

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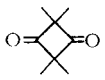
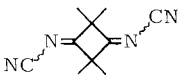
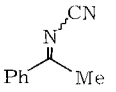
However, under these basic conditions the reaction fails in the case of, e.g., **5** (acid cleavage) and quinones **8**. These tend to undergo 1,4-addition and are more readily reduced than anthraquinone **8i**, which affords 62% **9i** with **2** and CsF.



5

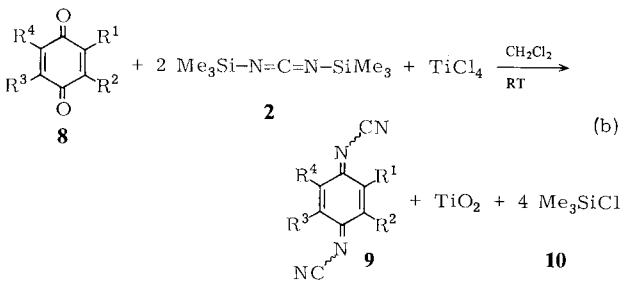


6 (47%)



7 (23%)

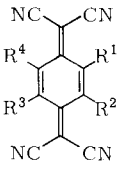
This problem can be overcome, however, by using titanium tetrachloride as auxiliary reagent. For example, **6** (47%, m.p. 143–144°C) can then be prepared quite smoothly, and even the enolizable acetophenone affords 23% **7**[3a], while *N*-cyanocyclohexanimine[1] is not detectable. Presumably the silyl groups are not eliminated as **4** in the presence of $TiCl_4$, but as **10** [cf. eq. (b)].



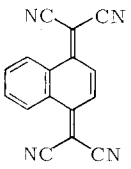
8 + 2 $Me_3Si-N=C=N-SiMe_3$ + $TiCl_4$ $\xrightarrow[RT]{CH_2Cl_2}$ **2** (b)

9 + TiO_2 + 4 Me_3SiCl **10**

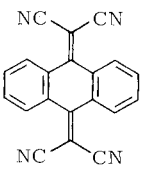
The first synthesis of the *N,N'*-dicyanoquinonediimines **9**[6] counts among the few reactions involving condensation at the carbonyl group of the quinones **8**. The selected examples **9a–i** demonstrate the broad spectrum of quinone substituents tolerated with regard to changes in potential and spatial requirements (Table 1).



11



11h



11i

sured in $\lg K_{SEM}$ values—frequently exceed even those of the quinone systems **8**. Because of the chemical analogy between the groups $=C(CN)_2$ and $=N-CN$[7], the systems **9** ("DCNQI") have acquired considerable importance as alternatives to derivatives of tetracyanoquinodimethane ("TCNQ") **11**, $R^1-R^4=H$, being acceptor components for electrically conducting CT complexes[8]. X-ray structure analyses of all the compounds reveal that the planarity required for this purpose is assured in the case of **9h**[8], and probably also in the case of **9a–g** and **9i**, but is not so in the analogues of **9h** and **9i**, the dicyanomethylene derivatives **11**[9] and **11i**[10].

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[4] L. Birkofer, *Tetrahedron Lett. 1962*, 195.
[5] Melting points and spectral data are in agreement with those quoted in the literature (cf. [3a] and [3b]).
[6] Procedure: Under exclusion of moisture, a solution of **8** in CH_2Cl_2 is treated consecutively with $TiCl_4$ and a solution of **2** in CH_2Cl_2 (both reagents in 2- to 25-fold excess). The reaction is monitored by thin-layer chromatography (SiO_2/CH_2Cl_2).—Work-up: a) The reaction mixture is filtered through a short silica gel column (10 cm Woelm 0.063–0.200 silica gel) and washed with CH_2Cl_2 (**9b**, **9c**).—b) The reaction mixture is poured into petroleum ether (30–75°C), the precipitate filtered off, extracted with benzene, and the product re-precipitated with petroleum ether (**9a**, **9h**).—c) After shaking with ice-water, the organic phase is dried over $MgSO_4$ and the product precipitated with petroleum ether (**9d**, **9e**).—d) After addition of CH_2Cl_2 and granulated active charcoal the mixture is stirred for a short while, filtered, and the product precipitated with petroleum ether (**9f**, **9i**).—e) The product precipitating is filtered off (**9g**).
[7] a) E. Allenstein, *Chem. Ber. 101* (1968) 1232; b) H. Köhler, B. Eichler, R. Salewski, *Z. Anorg. Allg. Chem. 379* (1970) 183; c) H. Köhler, B. Kotte, *Z. Chem. 13* (1973) 350.
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[9] F. Iwasaki, *Acta Crystallogr. B27* (1971) 1360.
[10] U. Schubert, A. Aumüller, S. Hünig, unpublished results.

Table 1. Yields, melting points and electrochemical data of the *N,N'*-dicyanoquinonediimines **9a–i**.

9	R^1	R^2	R^3	R^4	Yield [%] [a]	Procedure	M.p. [°C]	E_1[V] [b]	E_2[V] [b]	$\lg K_{SEM}$
a	H	H	H	H	64	[6b]	165	−0.26	+0.38	10.90
b	Me	H	Me	H	75	[6a]	320–321	−0.44	+0.17	10.30
c	Me	Me	Me	Me	49	[6a]	125–127	−0.40	+0.05	7.49
d	*t*Bu	H	*t*Bu	H	58	[6c]	241	−0.50	+0.16	11.20
e	OMe	H	OMe	H	84	[6c]	265	−0.45	+0.15	10.12
f	OMe	OMe	OMe	OMe	59	[6d]	172–173	−0.38	+0.21	9.90
g	Cl	Cl	Cl	Cl	26	[6e]	258	+0.16	+0.76	10.12
h	H	H	$-(CH=CH)_2-$		41	[6b]	255	−0.38	+0.28	11.19
i	$-(CH=CH)_2-$		$-(CH=CH)_2-$		34	[6d]	226–226	−0.46	−0.11	6.07

[a] After recrystallization. [b] In CH_2Cl_2, $[nBu_4N]BF_4$ as supporting electrolyte; Pt electrodes vs Ag/AgCl in CH_3CN.

According to the ^{13}C-NMR spectrum ($CDCl_3$), **9a** is present as a *syn/anti* mixture, whereas all 2,5-disubstituted derivatives (**9b**, **d**, **e**) have an *anti*-configuration, but 2,3-disubstituted derivatives (**9h**) a *syn*-configuration. Tetrasubstitution lowers the conversion barrier (*syn* ⇌ *anti*) to ≈ 12 kcal/mol.

9a–i form two-step, reversible redox systems in which the thermodynamic stability of the radical anions—mea-

Crystal Structure and Conductivity of a Novel Charge-Transfer Complex of *N,N'*-Dicyano-1,4-naphthoquinonediimine and Tetrathiafulvalene

By *Alexander Aumüller, Erich Hädicke, Siegfried Hünig*, Albin Schätzle,* and *Jost Ulrich von Schütz*

The discovery that the CT-complex **3** formed from tetracyanoquinodimethane (TCNQ) **1** and tetrathiafulvalene (TTF) **2**[1] exhibits high electrical conductivity has stimulated the synthesis and study of numerous variants[2]. Besides the introduction of substituents in **1** and **2**, the heteroatoms in the donor **2** have also been exchanged (S→Se), with the acceptors always containing $=C(CN)_2$ groups. The synthesis of a new class of quinonoid acceptors in which the $=C(CN)_2$ groups are replaced by $=N-CN$[3], allowed the construction of novel, potentially conductive CT-complexes (cf. Table 1).

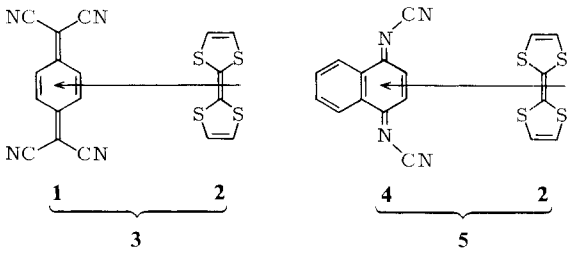

Table 1. Comparison of **3** with **5**.

	3	**5**
Conductivity [Ω^{-1} cm^{-1}]	192–652 [1a]	25
Distances in stack [pm]	317/347 [7]	329/353
Smallest distances between stacks [pm]	320 [7]	318, 324
Angle between acceptor- and donor-planes [°]	58.5 [7]	9

As first example, we describe here the CT-complex **5**[4], obtained from **2** and *N,N'*-Dicyano-1,4-naphthoquinonediimine **4**[3], which exhibits high conductivity and shows an ESR signal for ca. 10^{-2} mol/mol unpaired spins. Characteristically, the tetracyanonaphthoquinodimethane analogue of **4** does not form a CT complex with **2**, apparently due to the twisting of the molecule enforced on it by the Y-shaped $=C(CN)_2$ groups. This deformation does not take place in the *syn*-configurated **4**[4]. Thus, **5** obeys the rules outlined by *Cowan* et al.[5] for metallic conductivity of CT-complexes, both in the case of the reaction partners and, as shown by the crystal structure analysis, in the case of the crystal lattice (Fig. 1).

5 consists of separated, oblique stacks of almost planar donor and acceptor moieties, which are equidistant at room temperature. Since the distances in the stacks are only slightly greater than in **3**[7], there are also interactions here (distances between the moieties in solid **2**: 362 pm[7]). Contrary to **3**, the planes of the molecules in donor and acceptor stacks deviate very little from each other in **5**. An interaction between the negatively polarized N-atoms of the acceptor **4** and the positively polarized S-atoms of the donor **2** may be responsible for this, since the distance between these is the shortest in the stacks. The two terminal N-atoms of *one* acceptor molecule **4** are so coordinated with the S-atoms of *two* neighboring donor molecules **2** that the stacks form left- and right-handed helices in the crystal (Fig. 2).

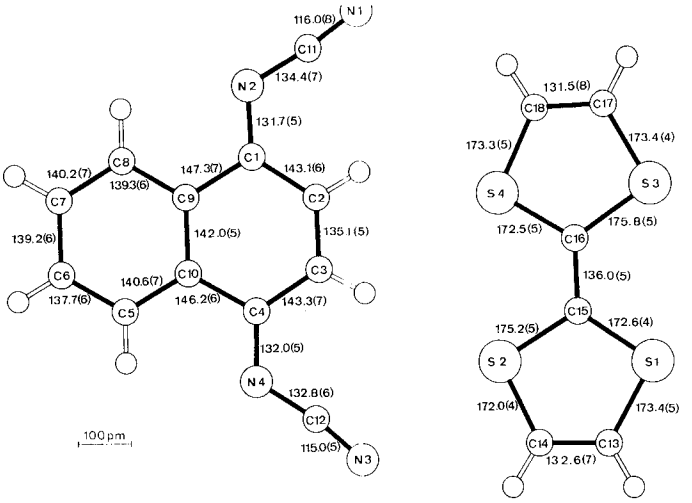

Fig. 1. Bond lengths [pm] of **4** and **2** in crystalline **5**.

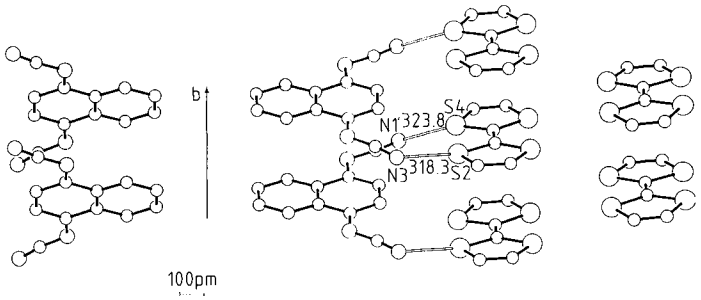

Fig. 2. Intermolecular contacts in crystalline **5** [pm].

The *syn*-configuration of **4** and the "inactivity" of the unsubstituted part of the naphthalene skeleton may be responsible for the special arrangement of the stacks: Two

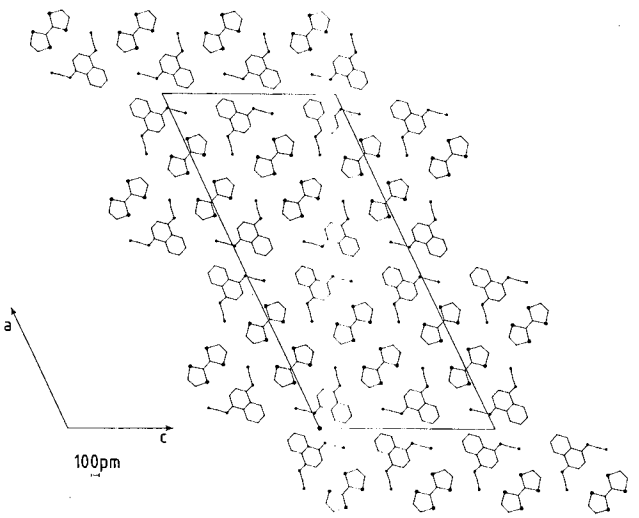

Fig. 3. *a/c* Projection of the crystal lattice of **5**.

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parallel, "back-to-back" rows containing stacks of **4**; "on the front side" there are two parallel rows of stacks of **2** (Fig. 3).

Figure 4 shows the temperature-dependence of the conductivity of **5**. The conductivity steadily increases with decreasing temperature down to a phase-transition temperature $T_c = 140$ K, and then decreases by several orders of magnitude down to 50 K. The temperature range above T_c is ascribed to metallic behavior, and that below T_c to semiconducting behavior with an activation of 0.08 eV (band gap 0.16 eV).

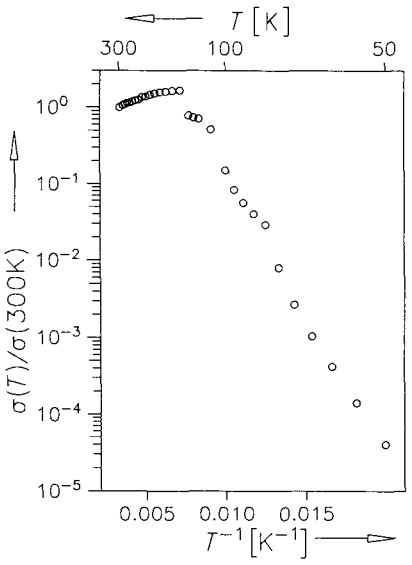

Fig. 4. DC conductivity of **5**. Four-point measurements on thin needles with single crystal domains.

The concentration of the mobile charge carriers, which could be deduced from the intensity of the ESR signal, was found to be ca. 10^{-2} spins/mol **5**, i.e. consistent with the values recorded for other similar salts.

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CAS-Registry number:
90343-29-6.

[1] a) J. Ferraris, D. O. Cowan, V. Walatka, Jr., J. H. Perlstein, *J. Am. Chem. Soc. 95* (1973) 948; b) L. B. Coleman, M. J. Cohen, D. J. Sandman, F. G. Yamagishi, A. F. Garito, A. J. Heeger, *Solid State Commun. 12* (1973) 1125.

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[3] Cf. A. Aumüller, S. Hünig, *Angew. Chem. 96* (1984) 437; *Angew. Chem. Int. Ed. Engl. 23* (1984) 447.

[4] Reaction of **4** with excess **2** in hot CH_3CN afforded **5** as black, shiny needles (up to 1 cm long), which are air-stable and gave correct analytical data.

[5] D. O. Cowan, A. Kini, L.-Y. Chiang, K. Lerstrup, D. R. Talham, T. O. Poehler, A. N. Bloch, *Mol. Cryst. Liq. Cryst. 86* (1982) 1.

[6] **5**: monoclinic, C2/c, $a = 4605.8(34)$, $b = 379.6(2)$, $c = 2183.4(14)$ pm, $\beta = 115.76(1)°$, $V = 3.4380 \times 10^9$ pm^3, $Z = 8$, $\rho_{calc} = 1.586$ g cm^{-1}, $\mu_{calc} = 50.9$ cm^{-1}; $Cu_{K\alpha}$ radiation (graphite monochromator), 2220 observed reflections, 1916 with $F_0 > 2\sigma(F_0)$, $R = 0.064$, $R_w = 0.049$. Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Energie, Physik, Mathematik, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD 50785, the names of the authors, and the journal citation.

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Peptide Structures of the Alamethicin Sequence: The *C*-Terminal $\alpha/3_{10}$ Helical Nonapeptide and Two Pentapeptides with Opposite 3_{10} Helicity**

By *Roland Bosch, Günther Jung*, Heribert Schmitt, George M. Sheldrick,* and *Werner Winter**

Alamethicin and its analogues are model compounds for the exitability of nerve membranes[1]. Voltage-dependent, ionophoric membrane pore formers of the icosapeptide antibiotic alamethicin-type contain numerous α-aminoisobutyric acid residues (Aib) which reduce considerably the conformation space. In oligopeptides with Aib residues, predominantly a tendency to form β-turns and 3_{10}-helical conformations (several consecutive β-turns III) is observed[2]. However, the structures of alamethicin[3] and of an *N*-terminal model undecapeptide[4] are α-helical. According to the flip-flop gating model[1], a rigid, preferably α-helical dipole is the only prerequisite for pore formation. Thus lipophilic peptide segments such as the sequential polymers Boc-(L-Ala-Aib-L-Ala-Aib-L-Ala)$_n$-OMe (n = 1–4) and the pentapeptide Boc-Aib-L-Ala-Aib-L-Ala-Aib-OMe **7** induce also voltage-dependent membrane pores since they form conformationally stable helix-dipoles in the lipid bilayers[1b].

1	Boc-Pro-Aib-Ala-Aib-Ala-OH
2	Z(Cl)-Pro-Aib-Ala-Aib-Ala-OMe
3	Tos-Aib-Aib-Aib-Aib-Aib-OMe
4	Z-Aib-Aib-Aib-Aib-Aib-O*t*Bu
5	Boc-Leu-Aib-Pro-Val-Aib-OMe
6	Z-Aib-Aib-Aib-Val-Gly-OMe
7	Boc-Aib-Ala-Aib-Ala-Aib-OMe
8	Boc-Aib-Pro-Val-Aib-Val-OMe
9	Boc-Leu-Aib-Pro-Val-Aib-Aib-Glu(OBzl)--Gln-Pheol
10	Boc-Pro-Aib-Ala-Aib-OBzl
11a	Ac-Ala-Aib-Ala-OMe
11b	Boc-Ala-Aib-Ala-OMe
12	Boc-Ala-Aib-Ala-Aib-Ala-Glu(OBzl)--Ala-Aib-Ala-Aib-Ala-OMe

Scheme 1. Aib peptides whose X-ray structures are known. Boc = *tert*-Butoxycarbonyl, Z(Cl) = *p*-Chlorobenzyloxycarbonyl, Bzl = Benzyl, Pheol = L-Phenylalaninol. All chiral amino acids have L-configuration.

In the following, we wish to describe interesting helical structures of the synthetic segments of naturally occurring membrane pore formers: **1** with a 3^1_{10}-helix (*N*-terminal alamethicin sequence 2–6), and **7**·2H_2O with a 3^r_{10}-helix (*N*-terminal suzukacillin A sequence 1–5)[2a], as well as the $\alpha/3_{10}$-helical structure of the *C*-terminal alamethicin nonapeptide 12–20 **9** (Scheme 1).

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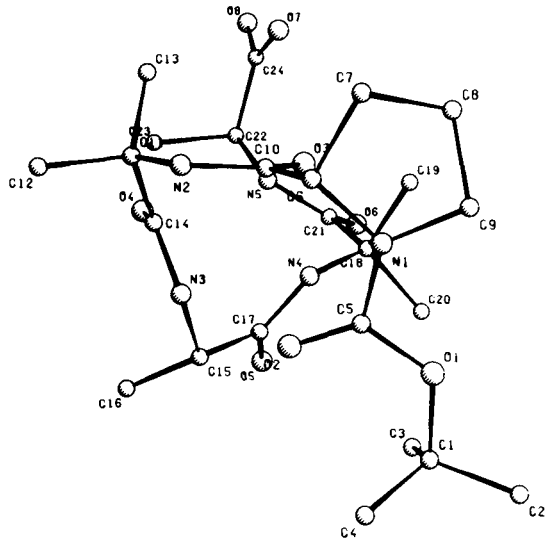
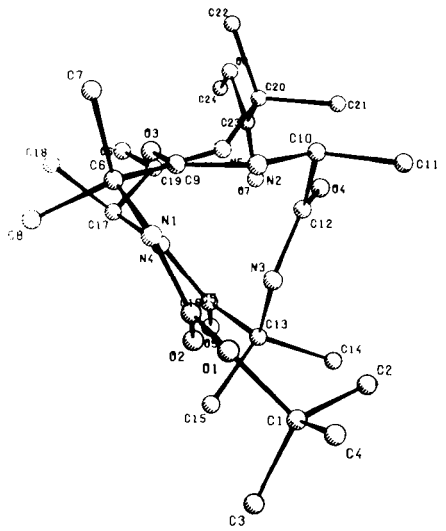
In the crystal, the pentapeptides **1** and **7** (Fig. 1) form 3_{10}-helices, each with three intramolecular (4→1) hydrogen bonds. Whereas **7** exhibits a *right-handed* helix with torsion angle combinations in the region $\phi = -60°$, $\psi = -30°$[2a], the helix in **1** is *left-handed* with $\phi = +60°$, $\psi = +30°$ (Fig. 2), although the chiral amino acids in both peptides have L-configuration. The assumption that the L-proline residue could cause the unusual left-handed helicity in **1** is not in harmony with the 3^r_{10}-helix of tetrapeptide **10**[2b].



1: Boc-Pro-Aib-Ala-Aib-Ala-OH

Handedness: , 3^l_{10} - Helix



7: Boc-Aib-Ala-Aib-Ala-Aib-OMe

Handedness: , 3^r_{10} - Helix

Fig. 1. Comparison of the inverse helical structures of **1** and **7**·2 H_2O [2a] (view direction: from N- to C-terminus, *N*-Boc protecting group at the bottom right corner). Structure solution of **1**: direct methods ($P2_12_12$, $Z=4$, $a=18.839(3)$, $b=18.776(7)$, $c=9.179(1)$ Å; CAD-4 diffractometer, $Cu_{K\alpha}$ radiation, room temperature); anisotropic structure refinement for C, N, and O (H isotropic); $R=0.056$ ($R_w=0.057$) for 2429 reflections with $F>0$.

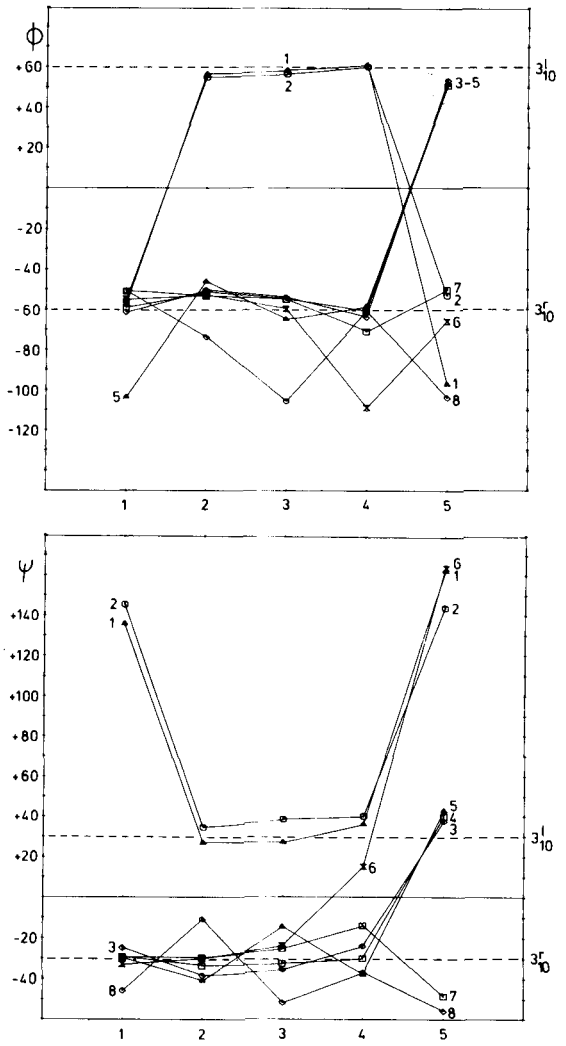


Fig. 2. Torsion angles ϕ and ψ [°] for Aib-containing pentapeptides: **1** (▲), **2** (○) [2e], **3** (◇) [2h], **4** (□) [2c], **6** (△) [2f], **5** (⧖) [2d], **7** (□) [2a], and **8** (◇) [2g].

In **1** the Boc-Pro urethane group is *trans*-orientated, although it normally prefers the *cis*-orientation[5]. According to model considerations, formation of the 3^l_{10}-helix from the *cis*-form would be impossible. Apart from **2**[2e], which is also a left-handed helix, no 3^l_{10}-structures are yet known. Protecting groups at the *N*- and/or *C*-terminus usually have only a slight effect on the secondary structure, as we find, inter alia, with **11a** and **11b**[6]. Particularly the segment Ala-Aib-Ala[6] appears to determine the structure of **1**, as indicated by comparison of the Aib torsion angles of **1** with those of the anomalous β-turn type of the tripeptides **11**: Aib^2 in **11** and Aib^4 in **1** have precisely the torsion angles of a 3^l_{10}-helix. Further evidence of the structural similarities is provided by the positive Cotton effects at $\lambda < 230$ nm for **11**[6]. The 3^l_{10}-helix of **1** (and its methyl ester) also shows small positive Cotton effects at $\lambda < 225$ nm and negative Cotton effects at $\lambda > 225$ nm, whereas the 3^r_{10}-helix of **7** shows qualitatively a mirror imaged CD curve.

The single intermolecular H-bond of **1** connects the molecules to linear chains in a head-to-tail fashion along [010], similar to that in **7**. However, the pentapeptide **7**, in contrast to **1**, forms a left-handed superhelix[2a]. Only lipophilic contacts occur between these parallely oriented,

one-dimensional superstructures; membrane-bridging, head-to-tail aggregates of this type might, therefore, also be the reason for the experimentally determined membrane pore formation by **7**. On the basis of CD and ^{13}C-NMR studies, we supposed earlier that for alamethicin-like sequences, e.g. $(Aib\text{-}Ala)_n$, a reorientation of the 3_{10}- to the more stable α-helix should occur in the region between the hepta- and the nonapeptide.—A recently described 3_{10}-helical decapeptide[2i] has a sequence which is less similar to that of alamethicin.

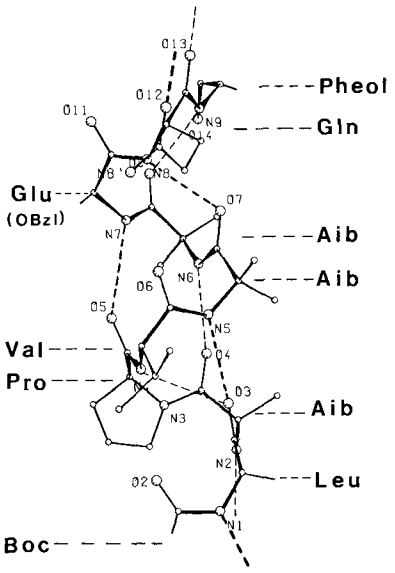


Fig. 3. Perspective view of the secondary structure of **9**. H-bonds are indicated by dashed lines, and bulky side groups are omitted. Structure solution: direct methods (SHELX 84 [7], refinement with SHELX 76 [7]; $P2_12_12_1$ $Z=4$, $a=15.666(6)$, $b=16.192(2)$, $c=25.876(3)$ Å); anisotropic structure refinement (H atoms isotropic), $R=0.063$ ($R_w=0.053$) for 5857 reflections with $F>0$). Four H_2O molecules per unit cell participate in the H-bonding scheme.

The structure of the *C*-terminal nonapeptide segment **9** of alamethicin in the crystal displays the interesting formation of 3_{10}- *and* α-helix regions in a longer Aib peptide (Fig. 3). Moreover, in connection with the α-helix of the *N*-terminal model undecapeptide **12** of alamethicin, which we described earlier[4], a direct structural comparison between the complete peptide antibiotic[3] and two structure-determining, longer segments is possible for the first time. The excellent agreement is illustrated in Figure 4. The right-handed helix extends beyond the proline residue over the total peptide length, as in alamethicin. Apart from two H-bonds, all the others are considerably longer than the ideal value of 2.9 ± 0.1 Å. In addition, two bifurcated H-bonds, which form both a C_{10}- as well as a C_{13}-turn, are observed. Of these, only the stronger components are shown in Figure 4. As in **12**[4], the individual molecules of **9** are linked head-to-tail by two intermolecular H-bonds to form antiparallel chains along [100]. An additional weak H-bond perpendicular to the helix results in the formation of a type of a layer-like structure; again only hydrophobic contacts occur between the layers.

NMR and CD studies indicate that, at least in chloroform and alcoholic solvents, this $\alpha/3_{10}$ helical conformation is retained. Negative Cotton effects at 223 and 207 nm form a CD spectrum which is typical for the dominant α-helix. We therefore postulate that the partial structure **9**, like alamethicin itself, also induces voltage-dependent ion-conducting membrane pores.

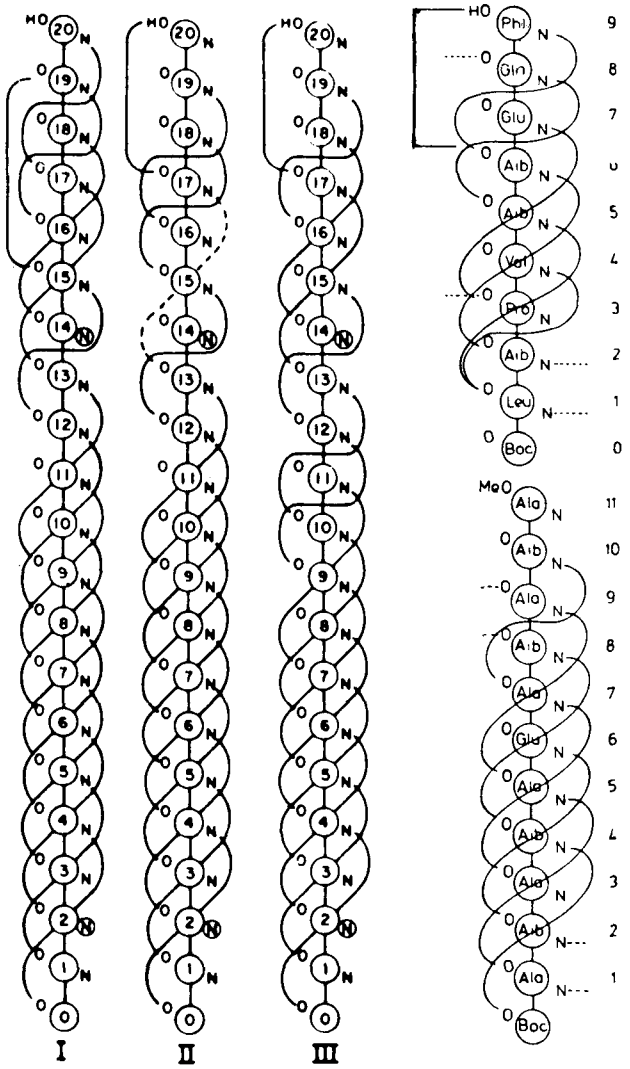


Fig. 4. H-bonding scheme for the three individual molecules of alamethicin (I, II, III) [3] compared with a combination consisting of the *N*-terminal model undecapeptide **12** [4] and the *C*-terminal nonapeptide **9** with natural sequence.

Our results, i.e. that alamethicin has predominantly an α-helical conformation, not only in the *C*-terminal part but also in the segment 12—20, should refute a recently published model[8]. In this model, a *C*-terminal, parallel β-pleated sheet structure was proposed on the basis of ^1H-NMR data, speculations having no experimental evidence, and the neglect of many known facts[1,3,4].

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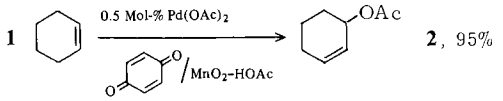
Oxidation with Palladium Salts: Catalytic Preparation of Allyl Acetates from Monoolefins Using a Three-Component Oxidation System**

By *Andreas Heumann** and *Björn Åkermark**

Because of their potential applications for the synthesis of complicated organic molecules[1] or merely of allylamines[2], the synthesis of allyl acetates is a topical problem, but is, however, only partly solved[3a]. In particular, the direct, metal-catalyzed oxidation of readily accessible monoolefins—a series of metals has been intensively studied[3b]—cannot be carried out in a selective and general way, although some alkenes can be converted in a highly designed way[3c].

We recently reported that, in the presence of a $PdCl_2$-$CuCl_2$ oxidation catalyst, 4-vinylcyclohexene derivatives react regio- and, in part, stereoselectively to afford allyl acetates[4]. A vinylic double bond appeared to be necessary for the successful, and in comparison to cyclohexene[5], very selective reaction (stabilization by intramolecular chelate). We have now found that monoolefins also react to give allyl acetates if another—combined with Pd^{II}—redox system is added[6]. Table 1 shows some experimental details for the reaction with cyclohexene **1**[7].



Other cycloalkenes (C_5, C_7, C_8, C_{12}) can also be converted into allyl acetates in the presence of 5% $Pd(OAc)_2$, but in somewhat lower yields (60—90%). Nonterminal aliphatic alkenes (e.g. *trans*-5-decene: 87%) also react similarly; however, in this case more regio- and configurational-isomers are obtained.

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Table 1. Catalytic preparation of 2-cyclohexenyl acetate **2**.

Catalyst	mol-%	Reoxidant	*T* [°C]	*t* [h]	Yield **2** [%]
$Pd(OAc)_2$	5	MnO_2	60	72	5
	5	*p*-benzoquinone	60	17	29
	5	*p*-benzoquinone/MnO_2 [a]	60	17	97
	0.5	*p*-benzoquinone/MnO_2 [b]	60	48	95
	5	chloranil/MnO_2 [c]	25	70	72
$PdCl_2$/AgOAc	5/10	TeO_2/*t*-BuOOH	25	72	32—44 [d]
$PdCl_2$		$CuCl_2$	75	2	88 [e]

[a] Pd : benzoquinone = 1 : 4. [b] Pd : benzoquinone = 1 : 10. [c] Pd : chloranil = 1 : 2. [d] Lit. [6b]: product contains varying amounts of 2-cyclohexen-1-one. [e] Lit. [8], Pd : Cu = 1 : 100, reaction up to 5% conversion of **1**.

p-Benzoquinone, a well-known reoxidation reagent for Pd^{II}-catalyzed functionalizations of conjugated dienes[9a], has only been used with moderate success with simple cycloalkenes[9b]. As found by *Bäckvall* et al. for the oxidation of conjugated double bonds[9a,c], addition of MnO_2[10], which under the reaction conditions is only capable of oxidizing the hydroquinone formed, but not Pd^0 or an alkene, permits the use of much smaller amounts of *p*-benzoquinone. Table 1 shows that *p*-benzoquinone markedly accelerates the reaction of monoolefins. Interestingly, substituted quinones can also be employed. Comparison with other acetoxylation reactions catalyzed by Pd indicates at least similar selectivities for cyclohexene and considerably higher selectivities for other cycloalkenes[5,6,8].

As is frequently observed for Pd-catalyzed oxidations[11], in this case the reoxidation system is of paramount importance. Quinone reacts highly probably as a ligand *and* reoxidant, and only the additional oxidizing agent (MnO_2) prevents—by rapid re-formation of the quinoid system—removal of the ligand from the palladium catalyst and hence precipitation of Pd^0.

These types of combined oxidation systems, which are often involved in biological processes, and by means of which two (or more) compounds that react extremely slowly and nonselectively with each other (olefin and acetic acid) are induced to react via a series of multiple catalyzed reactions, appear to be gaining more and more importance in organic chemistry[12].

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[7] *Procedure:* A mixture of $Pd(OAc)_2$ (2.24 mg, 0.01 mmol), *p*-benzoquinone (10.8 mg, 0.1 mmol) (Merck) and MnO_2 (174 mg, 2 mmol) (activated, Merck) in 10 mL glacial acetic acid is treated with **1** (164 mg, 2 mmol) and stirred intensively for 48 h at 60°C. After addition of water (5—10 mL), the resultant mixture is extracted 3 to 4 times with pentane.

The combined pentane phases are washed (2 × 2 M NaOH, 2 × H_2O) and dried ($MgSO_4$); pentane is removed in a rotary evaporator. The very pure (200 MHz, ^{1}H-NMR) and almost colorless crude product (250 mg) contains more than 95% **2**. Experiments on the 100 mmol scale (70 h) gave **2** in 95% conversion (GC: SE30, 80–160 °C, 4 °C/min) and ca. 80% yield upon distillation (m.p. = 69–70 °C/16 torr).

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Photochemical Generation of Triphenylsilylboranediyl ($C_6H_5)_3SiB$: from Organosilylboranes**

By *Bernd Pachaly* and *Robert West**

Organoboranediyls ("organoborylenes") are interesting in connection with questions of chemical bonding in hypovalent molecules and as reactive species. They have been postulated as intermediates in the photolysis of tri-1-naphthylborane[1] and in the dehalogenation of methylboron dibromide[2].

By photolyzing organobis(triphenylsilyl)boranes, such as **1** and **2**, or tris(triphenylsilyl)borane **3** in a hydrocarbon matrix at −196 °C, we have succeeded in generating triphenylsilylboranediyl and in detecting it via its subsequent reactions. This method had already proved useful for the preparation of hypovalent species in the chemistry of silicon[3].

Methyl-**1** and mesitylbis(triphenylsilyl)borane **2** can be obtained by reaction of the corresponding organoboron dibromides with triphenylsilyllithium.

$$RBBr_2 + 2\,Ph_3SiLi \xrightarrow[-10\,^\circ C]{THF/heptane} RB(SiPh_3)_2 + 2\,LiBr$$

1, R = CH_3
2, R = C_9H_{11}

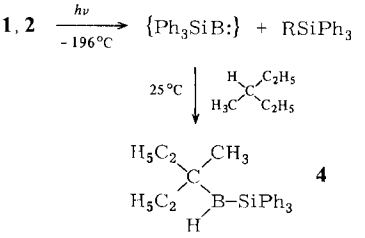
Tris(triphenylsilyl)borane **3** was prepared analogously[4].

$$BBr_3 + 3\,Ph_3SiLi \xrightarrow[-70\,^\circ C]{THF/heptane} B(SiPh_3)_3 + 3\,LiBr$$

3

The organosilylboranes **1**–**3** are colorless, moisture-sensitive solids which melt above their decomposition point (ca. 200 °C). Their IR spectra exhibit the characteristic stretching bands of the B–Si bond around 500 cm^{-1}[5]. In the mass spectrum[6], molecular ions and/or parent ions appear for all three compounds. Stepwise hydrolysis of **1** leads initially to cleavage of the B–C bond and subsequently to cleavage of the first B–Si bond, whereas mesitylboric acid is formed upon cleavage of the B–Si bonds of **2**; hydrolysis of **3** leads to boric acid.

Irradiation of **1** and **2** was performed in a 3-methylpentane matrix at −196 °C at $\lambda = 254$ nm. The absorption spectra of the irradiated matrix exhibited no characteristic new bands, except for a weak new band around 250 nm. In both cases, the insertion product 3-methylpentyl(triphenylsilyl)borane **4** was isolated and characterized as a reaction product[6].



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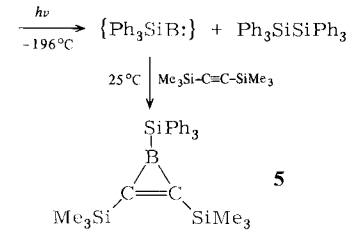
Compound **3** was irradiated in the presence of trapping reagents[7]. Upon cophotolysis with bis(trimethylsilyl)acetylene, 1-triphenylsilyl-2,3-bis(trimethylsilyl)borirene **5** can be isolated[6,8,9].



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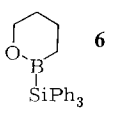
Analogous photolysis of **3** in the presence of tetrahydrofuran affords the insertion product, 2-triphenylsilyl-1,2-oxaborinane **6**[6].



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The reaction behavior of silylboranediyls indicates that they do not tend to dimerize, but that in the presence of trapping reagents insert, e.g. into the C–H or C–O bonds of solvent molecules.

The photochemical generation of this species could have application in the synthesis of organoboranes, possibly with boron-element double bonds—as indicated by the preparation of the borirene **5** and the oxaborinane **6**.

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[4] *Procedure:* A solution of BBr_3 (2.97 g, 0.012 mol) in 40 mL hexane is added dropwise to a solution of chlorobiphenylsilane (13.25 g, 0.045 mol) in 100 mL tetrahydrofuran (THF) containing lithium (3.15 g, 0.45 mol)—corresponding to approximately 0.04 mol Ph_3SiLi. After being stirred for 24 h at room temperature, the solvent mixture is removed, the residue taken up in 150 mL hot heptane and filtered. Upon cooling the filtrate to −15 °C, 6.0 g (64%) of **3** precipitates out as a white solid, and is recrystallized several times from heptane until a flame test indicates a Li-free product. In contrast, in the analogous preparation of **1** and **2**. Ph_3SiLi is added to the organoboron dibromides.

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[6] Analytical data: **1**: ^{1}H-NMR (Bruker WP 270, C_6D_6): $\delta = 0.35$ (s), 7.20–7.80 (m); IR (Perkin Elmer 457, *n*-heptane): ν_{BSi} [cm^{-1}] = 480 and 512; MS (Kratos MS 80, 30 eV, HR and PM): *m/z* 544 (M^+, 1.1%), 529 ($M^+ - 15$, 1.6%), 260 (32.2%), 259 (100%), 225 (9%), 199 (35%), 183 (31%); boron content (titrimetric after oxidative sample preparation): 1.79% (cal. 1.98%).—**2**: ^{1}H-NMR: 2.22 (s), 2.35 (s), 6.82 (s), 7.10—7.70 (m); IR: 512 and 530; MS: 648 (M^+, 1.0%), 529 ($M^+ - 119$, 5.1%), 333 (34%), 259 (80%), 199 (63%), 119 (100%); Boron content: 1.64% (calc. 1.76%).—**3**: ^{1}H-NMR: 7.10—7.70 (m); IR: 532; MS: 529 ($M^+ - 259$, 1.0%), 270 (529 – 259, 4.6%), 260 (75%), 259 (60%), 225 (19%); boron content: 1.44% (1.37%).—**4**: ^{1}H-NMR: 0.27 (s), 0.81 (m), 1.28 (t), 2.87 (s), 7.10—7.80 (m); IR: 515; MS: 341 ($M^+ - 15$, 4.9%), 260 (54%), 259 (100%), 97 ($M^+ - 259$, 28.4%), 82 (33%), 53 (12%).—**5**: ^{1}H-NMR: 0.46 (s), 7.20—7.92 (m); IR: 505; MS: 444 (M^+, 2.5%), 429 ($M^+ - 15$), 1.0%), 260 (25.7%), 259 (100%), 185 ($M^+ - 259$, 20.8%), 184 (42.3%), 183 (24.5%), 75 (9.7%), 59 (26.3%).—**6**: ^{1}H-NMR: 0.70 (t), 1.57 (m), 1.60 (m), 3.61 (t), 7.15—7.75 (m); IR: 512; MS: 342 (M^+, 2.0%), 259 (54%), 199 (100%), 119 (10%), 83 ($M^+ - 259$, 17%), 69 (57%), 55 (33%), 41 (28%), 28 (59%).
[7] *Procedure:* A thoroughly degassed solution of **3** (50 mg, 0.063 mmol) and bis(trimethylsilyl)acetylene (110 mg, 0.63 mmol) in 10 mL 3-methylpentane is irradiated in a low-temperature apparatus for 5 h at −196°C ($\lambda = 254$ nm). After thawing, precipitated hexaphenyldisilane is filtered off, and **5** is isolated from the solution as a yellow oil.
[8] The synthesis of a borirene via methylboronediyl has recently been described: S. M. van der Kerk, P. H. M. Budzelaar, A. van der Kerk-van Hoof, G. J. M. van der Kerk, P. von R. Schleyer, *Angew. Chem. 95* (1983) 61; *Angew. Chem. Int. Ed. Engl. 22* (1983) 48.
[9] In the absorption spectrum, **5** exhibits a band tailing to 450 nm. For the aromatic character of borirenes cf. K. Krogh-Jespersen, D. Cremer, J. D. Dill, J. A. Pople, P. von R. Schleyer, *J. Am. Chem. Soc. 103* (1981) 2589.

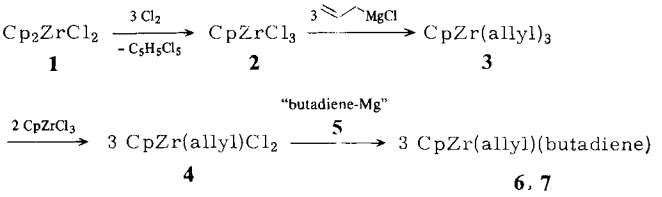
(η^3-Allyl)(η^4-butadiene)(η^5-cyclopentadienyl)-zirconium, a System of Isomeric Monocyclopentadienylzirconium(II) Compounds**

By *Gerhard Erker*, Klaus Berg, Carl Krüger, Gerhard Müller, Klaus Angermund, Reinhard Benn,* and *Gerhard Schroth*

Electronically unsaturated early transition-metal complexes are interesting substrates for the development of active catalysts for the CC coupling of olefins. Current examples contain the small number of compounds of the organometallic fragments (η-cyclooctatetraene)M and (η-pentamethylcyclopentadienyl)M (M = Ti, Zr, Hf)[1]. We have recently found a novel, general route to the mono(η-cyclopentadienyl)zirconium system[2]. This allowed us to synthesize the (η^3-allyl)(η^4-butadiene)(η^5-cyclopentadienyl)zirconium compounds **6**, **7**, to our knowledge the first isolated and structurally completely characterized mono(η-cyclopentadienyl)zirconium(II) system.

The radical chain chlorination of zirconocene dichloride **1** at 20—25°C in CCl_4 leads to $CpZrCl_3$ **2** (amorphous solid, 96%)[2]. Reaction with allylmagnesium chloride in ether at −40°C in a 1:3 molar ratio affords triallyl(η-cyclopentadienyl)zirconium **3**[3], isolated in 65% yield after extraction with pentane (−35°C) and crystallization (−78°C).

Above −10°C, **3** decomposes thermally. In the presence of zirconium halides it undergoes ligand exchange. A rather slow (72 h) comproportionation of **3** with $CpZrCl_3$ (molar ratio 1:2) at −40°C produces allyl(η-cyclopentadienyl)zirconium dichloride **4** (Scheme 1). The latter was not isolated, but reacted directly with "butadiene-magnesium" **5**[4b]. After usual work-up at room temperature and crystallization (pentane, −78°C), **6** is obtained as dark-red crystals (70% yield).



Scheme 1.

The molecular structure of **6** (Fig. 1) is derived from a square pyramidal geometry with an apical η-Cp ligand (Zr–C(Cp) = 2.512(7) Å) in which the η^3-allyl and the η^4-butadiene ligand both occupy basal positions. The molecular symmetry in the crystal is C_s. Normals to the planar carbon frameworks of all three π-ligands lie in the molecular mirror plane. As is often the case in complexes of this structural type[5], the open-chain π-ligands open towards the apex of the pyramidal framework. Parameters typical of the (η^3-allyl)Zr moiety are found[6] (Zr–C3 2.443(7), Zr–C4 2.446(8), C3–C4 1.440(8) Å, C3–C4–C3* 119.9(9)°). As expected for a zirconium complex, the bond lengths of the (*s-cis*-η^4-diene)metal moiety differ considerably from those of the corresponding moieties with more electron-rich late transition metals. However, values of 1.384(7) (C1–C2), 1.358(8) (C2–C2*), 2.360(5) (Zr–C1) and 2.463(5) Å (Zr–C2) point to a σ-complex character of **6** being decidedly less pronounced than in (*s-cis*-η^4-diene)$ZrCp_2$ complexes[7].

The NMR spectra of **6**[8] in addition to the ^{1}H-NMR-NOE difference spectra indicate that **6** adopts an analogous structure in solution. Dynamic behavior of the allyl

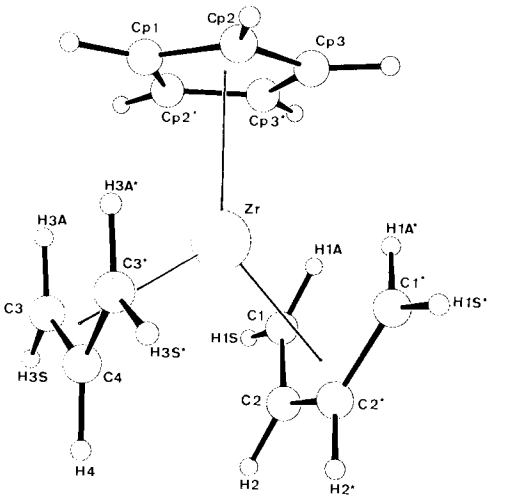


Fig. 1. Molecular structure of **6** in the crystal. Space group $P2_1/m$; $a = 7.412(1)$, $b = 11.335(2)$, $c = 7.5916(8)$ Å, $\beta = 117.699(7)°$, $V = 564.759$ Å^3, $Z = 2$, 1561 observed reflections, 64 parameters refined, $R = 0.051$, $R_w = 0.068$. Further details on the crystal structure analysis can be obtained from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, by quoting the depository number CSD 50786, the names of the authors, and the journal citation.

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[+] X-ray structure analysis; [++] NMR analysis.

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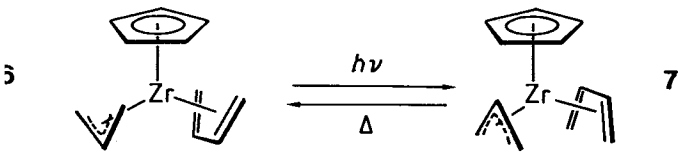
ligand is detected by ^{1}H-NMR spectroscopy (60 MHz) at high temperature (AA'BB'X→A_4X pattern, $\Delta G^{\ddagger}_{105\,°C} = 19.1 \pm 0.3$ kcal/mol, as estimated from the coalescence of the methylene protons[4a]).

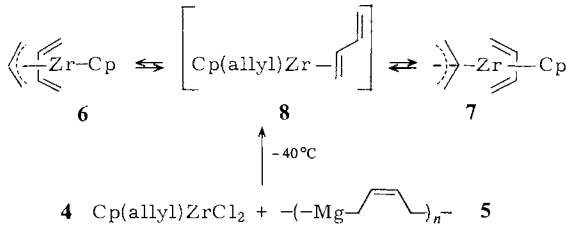
Photolysis of **6** (Philips HPK 125, Pyrex filter, toluene, −40 °C) leads to **7** in practically quantitative yield. Formation of this isomer can be monitored by the appearance of a new Cp singlet shifted to lower δ-values. Both the (*s-cis*-η^4-butadiene) ligand as well as the π-allyl moiety can be assigned by NMR[8]. According to the NMR data and the ^{1}H-NMR-NOE difference spectra, **6** and **7** are principally different with regard to the arrangement of the allyl and butadiene moieties relative to the Cp group: Both open-chain π-ligands in **7** open towards the base of the pyramidal framework (Scheme 2)[1a,9].



Scheme 2.

7 is only observed at sufficiently low temperature. Upon heating, **6** is re-formed in a smooth reaction. The thermally induced isomerization **7**→**6** follows a first-order rate law with $\Delta G^{\ddagger}_{10\,°C} = 22.1 \pm 0.2$ kcal/mol.

Reaction of CpZr(allyl)Cl_2 **4** with "butadiene-magnesium" **5** below −30 °C features a somewhat different result: even in the dark reaction **7** is formed in addition to **6** (55 : 45). Presumably, this reaction proceeds via intermediate **8**[10], which under kinetic control is stabilized by forming both isomers **6** and **7** with an almost equal probability (Scheme 3). It is possible that the thermally induced isomerization **7** ⇌ **6** might also proceed via **8**. However, from the experimental material presented it cannot unequivocally be distinguished between this mechanism of diene rotation and one involving a ring inversion process[7,11].



Scheme 3.

As shown by the example of the isolated complexes **6** and **7** in Scheme 1, a system of isomeric mono(η-cyclopentadienyl)zirconium(II) compounds of a square-pyramidal structural type has become readily available. These compounds become chiral[12] upon substitution at C1, C2, or C3 (see Fig. 1). Therefore their use in catalytic CC coupling reactions of the Ziegler-Natta type should be of particular interest.

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[3] **3**, ^{1}H-NMR ([D_8]toluene, −78 °C): $\delta = 5.10$ (s, 5H, Cp), 2.95 (d, 12H), 5.27 (m, 3H, allyl dynamic); IR (cyclohexane comp., 7C): $\nu = 1535$ (π-allyl), 1595 cm^{-1} (σ-allyl), cf. [4a].

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[8] **6**, ^{1}H-NMR ([D_8]toluene): $\delta = 6.04$ (Cp), −0.67 (H1A), 2.15 (H1S), 5.34 (H2), 1.23 (H3A), 1.81 (H3S), 6.05 (H4); ^2J(H1A,H1S) = −7.6 Hz, ^3J(H2,H2*) = 8.7, ^3J(H1S,H2) = 9.4, ^3J(H1A,H2) = 11.0, ^2J(H3A,H3S) = 1.4, ^3J(H3S,H4) = 9.1, ^3J(H3A,H4) = 14.6; ^{13}C-NMR: $\delta = 108.8$ (Cp), 45.8 (dd, 143, 154 Hz, C1), 112.5 (d, 160, C2), 56.8 (dd, 160, 146, C3), 125.5 (d, 153, C4). – **7**, ^{1}H-NMR ([D_8]toluene, −50 °C): $\delta = 4.62$ (Cp), −1.57 (H1A), 3.62 (H1S), 5.12 (H2), 0.94 (H3A), 3.26 (H3S), 6.08 (H4); ^2J(H1A,H1S) = −7.4 Hz, ^3J(H2,H2*) = 9.0, ^3J(H1S,H2) = 9.6, ^3J(H1A,H2) = 14.0, ^2J(H3A,H3S) = 1.8 Hz, ^3J(H3S,H4) = 8.7, ^3J(H3A,H4) = 15.8; ^{13}C-NMR: $\delta = 100.2$ (Cp), 48.4 (dd, 142, 158 Hz, C1), 99.9 (d, 156, C2), 55.6 (dd, 150, 160 Hz, C3), 117.2 (d, 148, C4).

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Ferrocenium Salts— The First Antineoplastic Iron Compounds**

By *Petra Köpf-Maier**, *Hartmut Köpf*, and *Eberhard W. Neuse*

Dedicated to Professor Ernst Otto Fischer

Metallocene dihalides of d-electron deficient transition metals such as $(\eta^5\text{-}C_5H_5)_2MX_2$ with M = Ti, V, Nb, Mo[1,2] or octahedral complexes such as *cis*-dihalobis(1-phenyl-1,3-butanedionato)titanium(IV)[3], for which antineoplastic activity has previously been detected, are neutral complexes and contain a *cis*-configurated MX_2 group; they are

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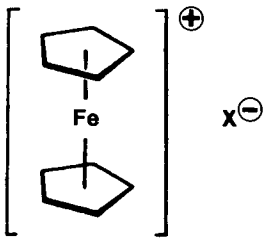
capable of releasing two neighboring coordination vacancies at the site of action, and, hence, fulfill structural conditions recognized as essential for cytostatic action and which are also realized by other inorganic or organometallic cytostatics[4,5].

In contrast, the ferrocenium salts $(\eta^5\text{-}C_5H_5)_2Fe^{\oplus}X^{\ominus}$ **1**[6,7], with the d-electron richer transition-metal iron as central atom, represent another type of coordinatively largely saturated complex in which the cyclopentadienyl ligands are not inclined to each other, but rather are arranged parallel to one another[8]. We have now surprisingly found that the cation in the salts **1** has antineoplastic activity.



1a: $X^{\ominus} = Cl_3CCOO^{\ominus} \cdot 2\,Cl_3CCOOH$[9]
1b: $X^{\ominus} = 2,4,6\text{-}(NO_2)_3C_6H_2O^{\ominus}$[7]
1c: $X^{\ominus} = FeCl_4^{\ominus}$[10]

To test the antineoplastic activity, we intraperitoneally (i.p.) implanted female CF1 mice with approximately 6×10^6 Ehrlich ascites tumor cells. After 24 h, the animals were administered various doses of **1a**, **1b**, or **1c** (20, 40, 60 ... 500 mg/kg; six animals per dose); the salts, which are readily soluble in water, were applied i.p. in physiological saline solution. Twelve control animals received an i.p. injection of 0.5 mL pure saline solution 24 h after implantation of the tumor cells. The animals were observed for 90 days after tumor transplantation; evaluation of the experiment was carried out as described in [4].

All three ferrocenium salts investigated had an inhibiting effect towards Ehrlich ascites tumor and, in optimal doses, cure 60 to 100% of the animals treated (cf. Fig. 1 and Table 1; for comparison, *cis*-$(NH_3)_2PtCl_2$, 10 mg/kg: 100% cure rate[4]); in the optimal dose range, the increase in mean survival time until the key-date is statistically highly significant (two-sided U-test, after *Wilcoxon*) relative to that of the untreated animals (15.3 d). Antineoplastic properties were neither detected for ferrocene $(\eta^5\text{-}C_5H_5)_2Fe$ **2** itself, nor for the tetrachloroferrates(III) $[(CH_3)_4N]^{\oplus}[FeCl_4]^{\ominus}$ **3a** and $[C_6H_5CH_2(C_2H_5)_3N]^{\oplus}[FeCl_4]^{\ominus}$ **3b**.

Our results permit the following conclusions to be drawn: 1) Not only metallocenes of the "early", but also of "middle" transition elements, such as iron, can effect cytostatic activity. 2) A coordination-gap releasing MX_2 group is not absolutely necessary for the realization of antineoplastic properties by metal complexes. 3) For this purpose, the occurrence as a neutral complex is also not a conditio sine qua non; in contrast, the excellent solubility of the salts in water, caused by the ionic character of **1**, proves to be propitious for applications in biological systems.

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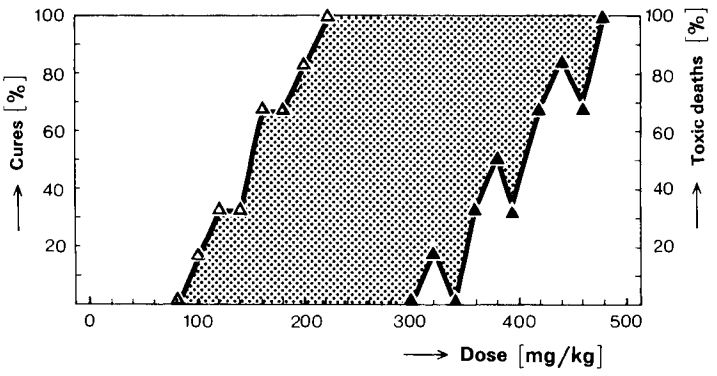

Fig. 1. Dose-effect curve (△—△) and dose-lethality curve (▲—▲) for **1a**; □ surviving animals on day 90. LD_{50} of **1a**: 400 mg/kg.

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Table 1. Pharmacological data for the iron complexes investigated against Ehrlich ascites tumor in mice.

Compound	Solvent [a]	Dose range studied [mg/kg]	Optimum dose range (=OD) [mg/kg]	Cure rate in the OD [%]	Mean survival time in the OD [d]	LD_{50} [mg/kg]
1a	s	20, 40, ..., 500	220—300	100	90	400
1b	s	20, 40, ..., 500	220—240	100	90	340
1c	s	20, 40, ..., 500	180—200	67	65	240
2	p	20, 40, ..., 500	—	—	—	440
3a	s	4, 8, 12, 16; 20, 40, ..., 500	—	—	—	80
3b	s	4, 8, 12, 16; 20, 40, ..., 500	—	—	—	120

[a] s = 0.9% NaCl solution (max. 0.4 mL/mouse); p = propylene glycol (max. 0.1 mL/mouse).

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Highly Enantioselective Alkylation of Tetrahydroisoquinolines via a Valine Chiral Auxiliary; Asymmetric Synthesis of (*S*)-Isoquinoline Alkaloids

By *A. I. Meyers**, *Michael Boes*, and *Daniel A. Dickman*

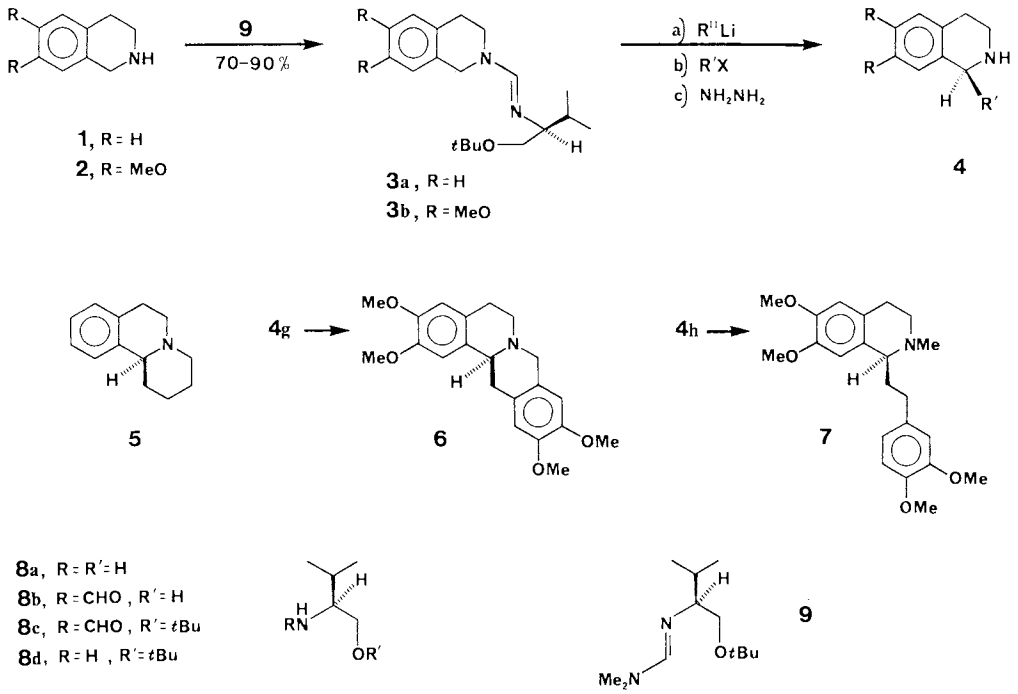
The utilization of natural amino acids as a source of chirality for the preparation of various enantiomerically enriched compounds has been reviewed recently[1]. We have reported that tetrahydroisoquinolines, via their *N*-iminomethyl derivatives (i.e. as formamidine derivatives), are metalated and alkylated to give 1-alkyltetrahydroisoquinolines in good yields[2,3], while enantioselective alkylations via chiral formamidines provide these products in high enantiomeric excess[4]. These enantioselective alkylations were performed using the disilyl ethers of (1*S*,2*S*)-(+)-2-amino-1-phenyl-1,3-propanediol, whose availability and stability posed some technical problems. We now report that the *tert*-butyl ether **8d** of valinol **8a** can not only be conveniently prepared, but also leads to higher enantioselectivity than the propanediol derivative when transformed into the formamidine **9**. By simple exchange between the isoquinolines **1** or **2** and **9**, the chiral formamidines **3a** or **3b** are obtained in 70—90% yield[5]. Metalation with lithium diisopropylamide (for **3a**) and *tert*-butyllithium (for **3b**) gave the lithiated formamidines, which were alkylated with alkyl halides and then hydrazinolyzed to remove the iminomethyl group[6]. The high efficiency of this process is outlined in Table 1. The enantiomeric excesses of **4** were determined by chiral-column HPLC analysis, as developed by *Pirkle*, and applied to chiral *N*-heterocycles and other amines[7,8]. The optical rotations in Table 1 were obtained on purified **4**. The amines were released from the recrystallized hydrochlorides **4** · HCl, converted into *N*-(α-naphthoyl)amides, and resubjected to HPLC analysis. These derivatives showed >99% enantiomeric purity, and thus the rotations are for pure materials. Clearly, recrystallization of the hydrochlorides increased the optical purity of **4**.

Several naturally occurring isoquinoline alkaloids were prepared using this method. Thus (−)-salsolidine **4f**[9] was formed from **3b** and MeI (Table 1), whereas (−)-norcoralydine **6** ($[\alpha]_D$ −273, $c = 1.17$, $CHCl_3$) was obtained in 98.5% *ee* by cyclizing **4g** (from **3b** and dimethoxybenzyl bromide) with formaldehyde and 2 N HCl (reflux, 30 min)[10]. The alkaloid (*S*)-(+)-homolaudanosine **7**, recently isolated[11], was readily prepared from **3b** and dimethoxyphenethyl iodide to give the corresponding 1-substituted isoquinoline, which was *N*-methylated (46%, ethyl formate, $LiAlH_4$) to the natural material [(α]$_D$ 10.4°, $c = 0.2$, $CHCl_3$). Finally, the benzoquinolizidine **5**, a degradation product of securine, was prepared by treatment of **3a** with 1-bromo-4-chlorobutane, which cyclized to **5** concurrently

Table 1. Synthesis of (*S*)-1-alkyl-1,2,3,4-tetrahydroisoquinolines **4** [6].

Educt [a]	R′X	Product	Yield [%] [b]	$[\alpha]_D$ [c]	*ee* [%] [d]
3a	MeI	**4a**	50	−71.3° (0.64)	99
3a	*n*BuI	**4b**	56	−78.4° (0.96)	96
3a	AllylBr	**4c**	63	−83.1° (0.61)	96
3a	$PhCH_2Cl$	**4d**	66	−62.2° (1.24)	98
3a	$PhCH_2CH_2Br$	**4e**	67	−23.5° (5.71)	93
3b	MeI	**4f**	61	−56.5° (4.15) [e]	95
3b	$3,4\text{-}(MeO)_2PhCH_2Br$	**4g**	75	[f]	99
3b	$3,4\text{-}(MeO)_2PhCH_2CH_2I$	**4h**	75	[f]	95

[a] **3a** was metalated with 1.05 equiv. $LiN(iPr)_2$ in THF at −78°C; **3b** was metalated with 1.1 equiv. *t*BuLi (2.3 M in THF). [b] Based on overall yield for **3**→**4**. [c] Based on amine released from hydrochloride salts after recrystallization. The values reflect optical purities >99%, as determined by chiral HPLC analyses of the *N*-(α-naphthoyl)amides. [d] Determined by chiral HPLC analyses of the *N*-(α-naphthoyl)amides from products obtained by metalation-alkylation *before* purification of hydrochloride salts. [f] In EtOH; cf. [9]. [f] Not determined since **4g** and **4h** were carried forward to **6** and **7**, respectively. Enantiomeric excess was determined through the *N*-(α-naphthoyl)amides and comparison with the rotation values of the natural products [10, 11].



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with hydrazinolysis (50—60%, $[\alpha]_D$ −206°, c = 0.017, pyridine, 93—95% *ee*)[12].

The asymmetric synthesis described here provides the (*S*)-enantiomer of all the products obtained, as indicated by comparison of the absolute configuration of the natural isoquinolines, and should provide ready access to a wide variety of enantiomerically pure isoquinoline alkaloids.

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[5] Procedure for **9** and **3**: Valinol **8a** was treated with excess ethyl formate (reflux, 3 h) and concentrated to afford crude **8b**, which was stirred with excess isobutene (0°C, dioxane, trace of H_2SO_4, 3 equiv. $BF_3 \cdot OEt_2$) for 3 h and gave, after kugelrohr distillation, the ether **8c** (92%, $[\alpha]_D^{25}$ −55.7, c = 1.08, tetrahydrofuran (THF)). Hydrolysis of **8c** with 1:1 of 50% KOH ethanol (reflux, 4 h) gave the crude amine **8d**, which was dried prior to addition of 1.1 equiv. $Me_3NCH(OMe)_2$, and heated at 50° for 12 h. Concentration and kugelrohr distillation (70°C/0.03 torr) gave **9** (80% $[\alpha]_D^{25}$ −15.9°, c = 0.98, THF). **3a** and **3b** were formed by heating **1** or **2** with 10—50% excess **9** in toluene for 48 h and concentrating the solution. The residue was first chromatographed (silica gel, 5% Et_3N-hexane) and then distilled (kugelrohr) to give **3a** and **3b** as oils. Correct elemental and spectral analyses were obtained; $[\alpha]_D$ −3.96, c = 1.06, THF, and −30.3, c = 2.7, $CHCl_3$, respectively.
[6] Procedure for **4**: A 0.03 M solution of **3** in THF was lithiated at −78°C. The deep red solution was cooled to −100°C and the alkyl halide added. After 30 min the reaction was quenched in CH_2Cl_2–H_2O, and the organic layer dried (K_2CO_3) and concentrated. The residue was dissolved in 60% aqueous ethanol (3 mL/mmol) and 3—5 equiv. hydrazine and 3—5 equiv. acetic acid added. After being stirred at 25°C or refluxed overnight, the mixture was quenched in CH_2Cl_2–H_2O. The organic layer was dried (K_2CO_3), concentrated, and distilled (kugelrohr). For *ee*-determinations, the *N*-(α-naphthoyl)amides of **4** were prepared and analyzed by HPLC [7].
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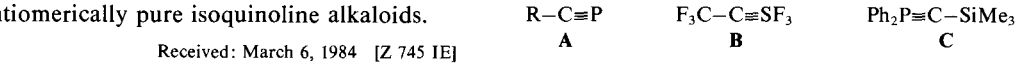
First Evidence for an Intermediate Nitrilo-λ^5-phosphane $>P\equiv N$**

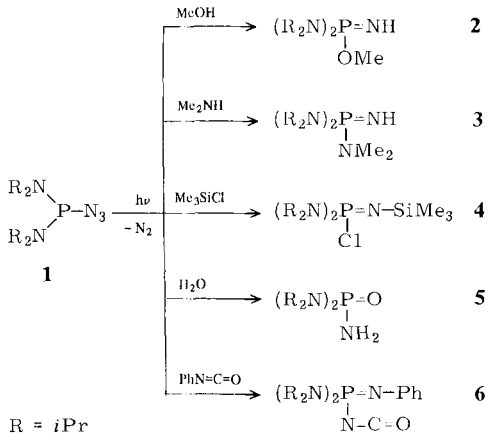
By *Ghislaine Sicard, Antoine Baceiredo, Guy Bertrand**, and *Jean-Pierre Majoral**

During the last twenty years, one of the most fascinating areas in the chemistry of the heavier main group elements has been the synthesis and reactivity of p_π-p_π multiply bonded compounds[1]. Whereas a number of investigations have been devoted to double bonded derivatives, in contrast, only a few reports have appeared on compounds possessing a triple bond between elements of the first and the second rows of the periodic table: some phosphaalkynes **A**[1c], the trifluoroethylidynesulfur trifluoride **B**[1f], and only one transient λ^5-phosphaacetylene **C**[2].



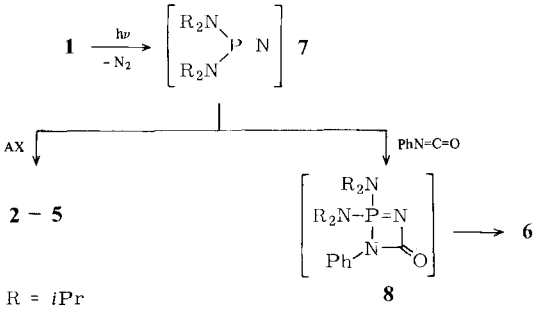
Recently, ab initio effective potential calculations indicated that the structure of singlet λ^3-phosphinonitrene H_2P–N is better formulated as a nitrilo-λ^5-phosphane $H_2P\equiv N$ due to delocalization of the lone pairs $n_\pi(P) \rightarrow p_\pi(N)$ and $n_\pi(N) \rightarrow d_\pi(P)$[3]. These findings prompted us to investigate the possibility of generating a "λ^3-phosphinonitrene–nitrilo-λ^5-phosphane" by photolysis of an azidophosphane.

We chose to study the photochemical behavior of azidobis(diisopropylamino)phosphane **1**[4] in order 1) to prevent Staudinger reactions by steric effects[5], and 2) to avoid formation of a tricoordinated λ^5-phosphane R_2N–$P(=NR)_2$[6] by using poor migrating groups.



1 was photolyzed at room temperature in benzene at λ = 300 nm[7] in the presence of a stoichiometric amount of trapping agent AX. Products **2** to **6** were obtained in near quantitative yield[8].

It seems reasonable to postulate that compounds **2** to **5** result from 1,2-addition of the trapping agent AX to the phosphorus-nitrogen triple bond of an intermediate bis(diisopropylamino)nitrilo-λ^5-phosphane **7**. The diamino(imino)isocyanato-λ^5-phosphane **6** probably arises from [2+2]-cycloaddition of phenyl isocyanate to **7** followed by ring opening of the resulting strained cyclic adduct **8**.



1,1-Adducts of type **9** were not observed, and we therefore note that they cannot be the precursors of products **2**

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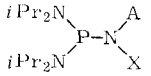

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to **5**. Moreover, no trapping reactions occurred when monoolefins, conjugated dienes, or dimethyl sulfide were used. These results, as a whole, showed that the λ^3-phosphinonitrene reacts as a nitrilo-λ^5-phosphane. This is in perfect agreement with the calculated structure with a polarized phosphorus-nitrogen triple bond[3]. It is noteworthy that, in contrast to tetra- or pentacoordinated phosphorus azides[9], no Curtius rearrangement takes place, supporting the stabilization of the nitrene.

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Nickel-Catalyzed Reduction of Carbon Monoxide by Hexamethyldisilane: a New Reaction Leading to a Novel Synthesis of Siloxanes**

By *K. Peter C. Vollhardt** and *Zhen-Yu Yang*

The oxophilicity of silicon[1] has been exploited in a number of organic transformations[1,2]. Particularly intriguing are reports on the oxidation of disilanes with a variety of oxidizing agents to furnish siloxanes[3]. These observations, in conjunction with the hydrogen-like reactivity of disilanes in the presence of transition metals[2,4], suggested the attractive possibility of utilizing hexamethyldisilane **1** as a reducing agent for carbon monoxide, a fundamentally new transformation potentially analogous to the Fischer-Tropsch reaction[5], but leading to silicon-containing products. We report that 50% nickel on kieselguhr does indeed mediate this reaction, furnishing siloxanes and surface-deposited carbon:

$$\underset{\mathbf{1}}{R_3Si{-}SiR_3} + CO \longrightarrow \text{"C"} + \underset{\mathbf{2}}{R_3SiOSiR_3} + R_3SiOSiR_2OSiR_3 \cdots$$

In the presence of hydrogen this carbon is converted into methane. The results of a series of experiments and the experimental conditions are delineated in Table 1.

Table 1. Major products from the reaction of CO and $Me_3SiSiMe_3$ **1** in the presence of 50% Ni-kieselguhr [a, b].

Run	Changes in conditions	Conversion of **1** [%]	$(Me_3Si)_2O$	Yield [%] Siloxane (total)	CH_4 (in gas phase)
1	—	62.4	25.8	35.6	7.3
2	170°C	[c]	4.1	6.5	[c]
3	250°C	72.0	33.2	41.8	[c]
4	no CO, (carrier gas N_2)	12.6	2.0 [d]	3.6 [d]	trace
5	with H_2 ($CO:H_2 = 1:1$)	91.8	59.0	68.0	42.1 [e]
6	batch reaction [f, g]	26.1	10.3	18.8	6.0
7	Et_3SiH instead of **1**	94.0 [h]	57.0 [i]	57.0	10.3 [j]

[a] United Catalysts Inc.; C46-7-01. [b] Conditions: flow system; catalyst 8.0 g; 200°C; 1 bar; HMDS 1.6 mL h^{-1}, added by syringe pump; CO 900 mL h^{-1}; time on stream: 2 h. [c] Not quantified. [d] Impurity in commercial **1** (Alfa). [e] Yield based on CO. [f] Solvent, xylene (10 mL), 100 mL Fischer-Porter glass bomb; catalyst 1 g; 180°C; $p(H_2) = p(CO) = \approx 2.45$ bar at RT; **1**: 0.73 g; reaction time 20 h. [g] A similar result was observed using decalin as solvent. [h] Conversion of triethylsilane. [i] Yield of hexaethyldisiloxane. [j] In addition to methane, ethane was formed.

The major silicon-containing product in most cases (exceptions are runs 4 and 6, cf. Table 1) was hexamethyldisiloxane, but, clearly, substantial amounts of higher molecular weight products were formed. Careful analysis (GC-MS; preparative GC; spectral identification by comparison with authentic materials) revealed the presence of higher siloxanes. A typical product distribution (run 1) was: tetramethylsilane (0.2%), hexamethyldisiloxane (38.3%), unreacted hexamethyldisilane (46.9%), hexamethylcyclotrisiloxane (5.0%), octamethyltrisiloxane (5.2%), and decamethyltetrasiloxanes (1.3%), in addition to traces of other materials. The proportions of these products do not change, but the activity of the catalyst decreases with time. The observation of higher siloxanes is important in light of the commercial significance of silicones[6]. We do not know yet whether these products are generated through direct oxidative Si–C bond cleavage or catalyzed redistribution[7]. In this connection, we have found that doping the reaction with hexamethyldisiloxane gave relatively more of the higher siloxanes.

In the absence of CO, only a certain amount of decomposition of **1** was noted[8] (run 4). The efficiency of siloxane formation increased dramatically in the presence of added H_2 (run 5), with the concomitant emergence of me-

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thane in good yield. A similar increase in activity was observed when using triethylsilane (run 7), which furnished only hexaethyldisiloxane as oxidation product[9]. On the other hand, a batch reaction revealed decreased catalyst efficiency in terms of conversion of **1**, although a much higher production of higher siloxanes (run 6) was noted, in a ratio similar to that obtained under flow conditions.

In order to pinpoint the origin of the component atoms in the methane formed, as well as that of the oxygen in the siloxanes, several labeling experiments were performed. Execution of run 5 (Table 1) with D_2 instead of H_2 gave mainly CD_4 (84%) in addition to some protic (predominantly CH_3D) methane. None of the silicon-containing products (and **1**) showed incorporation of deuterium. Similarly, use of ^{13}CO gave mainly $^{13}CH_4$ (84.4%) and revealed the absence of ^{13}C in the other product molecules. Thus, clearly, the major contributors to methane formation are CO and H_2, minor amounts arising from **1** and siloxane decomposition or as part of the pathways which lead to higher siloxanes.

Since it was of interest whether the oxygen in the siloxane product was, in fact, somehow derived from the kieselguhr support or other oxygen sources, an additional control was carried out involving $C^{18}O$. This experiment revealed completely clean incorporation of ^{18}O into all isolated siloxanes.

Mechanistically, it is tempting to formulate surface pathways analogous to those found in the Fischer-Tropsch reaction[10], involving not only CO and H–H, but also Si–Si and Si–C activation on the nickel surface. Current work is directed at further mechanistic elucidation of the pathways controling these unprecedented transformations and at finding other substrates for the carbon left after it has been stripped of its oxygen by **1**.

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BOOK REVIEWS

The Chemistry of the Allenes. Edited by *S. R. Landor*. Academic Press, London 1982. Vol. 1: Synthesis, p. 1–234, bound, $ 66.00; Vol. 2: Reactions, p. 235–578, bound, $ 86.00; Vol. 3: Stereochemical, Spectroscopic and Special Aspects, p. 579–882, bound, $ 86.00. Each volume contains index to whole work (pp. 26).

The subjects of all three volumes are presented in a short introduction (Chapter 1, 17 pp.) in Volume 1 by *S. R. Landor*. The remainder of the first volume is devoted to *P. D. Landor*'s description of allene synthesis. Chapter 2 deals with the synthetic methods for the hydrocarbons, for halogenated allenes, then for allenes containing alcohol, ether, aldehyde, ketene, carboxylic acid and carboxylic acid derivative functions, and finally for allenes bearing heteroelements (B, Si, Sn, N, P, S, Se, Te). The shorter, third chapter covers the synthesis of allenes containing additional olefinic, acetylenic or allenic functions. Each class of substance is dealt with in a separate section with an independent reference list. It is here that the need for an additional author index (with reference number and page number) becomes apparent, with which to keep track of allenes with several functional groups and to keep a better check on the comprehensiveness of the literature citations. This applies not only to this volume devoted to synthesis, but to the whole series, since a complete author index allows the rapid tracking down of a whole range of publications which describe not just the synthesis of allene derivatives but also their reactivities and/or other properties. Random sampling of the synthesis volume revealed that the literature citations (up to 1980), though not comprehensive, do at least cover the most important literature. The text does not reveal whether comprehensiveness or a review of the most important methods was the intention. Nor are the somewhat older but excellent reviews of various aspects of allene chemistry referred to. In the interests of a clearer conspectus the reviewer would like to have seen a distinction made in the various sections between reactions in which allenes merely undergo transformations without the cumulene being affected or altered and syntheses where the cumulene is actually created. A classification according to mechanism would have been preferable to the formal one used: For instance, Section 2.3.1 on the synthesis of allenic alcohols ("Reduction Methods") deals with the addition of hydride ions to 1,3-enynes, the addition of a hydride ion to the carbonyl group of allenic ketones and the nucleophilic substitution (S_N2') of halogen atoms in the propargyl position by hydride ions, while in Section 2.3.4 ("Use of Organometallic Reagents") the reaction of allenic Grignard reagents with ketones, of Grignard reagents with allenic ketones, and the fragmentation of tosyl hydrazones by butyllithium are discussed as well as the reaction of organometallic compounds with propargyl halides and suitable epoxides. The addition of organometallic compounds to 1,3-enynes is dealt with separately in Sec-

tion 2.3.3. The hydroxyalkylation of an allene ether with butyllithium and 3-pentanone described at the end of this section does not belong here. This criticism, however, applies only to the arrangement and not to the content. The author has presented the methods scientifically correctly and has also given a critical indication of the limits and applicability of the methods.

S. R. Landor covers the substitution reactions of 1- or 3-, 4-, and 5-halo-1,2-alkadienes in Chapter 4 (Volume 2). The most interesting reactions are those of the 1-halogen derivatives with geminal hydrogen atoms, since these can yield allenic carbenes by 1,1-elimination under the influence of strong bases. These carbenes can react with nucleophiles by undergoing 1,1- or 1,3-addition or are captured by olefins (see also Section 2.1.1, c) with the formation of allenylidenecyclopropanes. After the relatively short but informative report by *H. Hopf* on sigmatropic rearrangements of stable allenes, *T. L. Jacobs* discusses the transition metal complexes of the allenes. A list with literature citations and commentaries makes possible a rapid overview of the allenic complexes that have so far been isolated; then follows a discussion of their synthesis, structure and stereochemistry. The oligomerization and polymerization reactions of the metal complexes described at the end should be of interest to organic chemists, too. It can be seen from the reference list that this is a very new field; most of the references appeared in the 1970s, the majority of them towards the end of the decade. Chapter 5 (Volume 2) summarizes practically all the types of allene additions and cycloadditions: First *S. R. Landor* reports briefly on reactions with carbenes, which lead to a wide range of interesting cyclopropanes, and then on the nucleophilic addition of hydride ions and organometallic compounds. After a short section on radical additions *T. L. Jacobs* presents the large field of electrophilic additions. The tables which summarize the reactions with protonic acids, sulfenyl chlorides, halogens and with mercury salts are very useful for gaining a preliminary overview. These are followed by the mechanistically interesting epoxidation reactions; the methyleneoxiranes formed initially are only isolable with bulky residues. The last three sections of Chapter 5 contain a survey of allene cycloadditions. While the number of reactions with 1,3-dipoles is relatively limited *(S. R. Landor)*, [2+2]-cycloadditions seem of greater importance. Their preparative and mechanistic development between 1970 and 1979 is described by *H. Hopf*; he cites reviews on earlier work. In the section on [4+2]-cycloadditions he points out that vinyl-substituted allenes and bisallenes react as dienes, while simple allenes function as dienophiles.

Chapter 6 in Volume 3, concerning the stereochemistry of allenes, is particularly worthy of mention. In it *W. Runge* first of all explains the phenomenon of allene chirality, then takes up the synthesis of chiral allenes, and finally mentions some chosen reactions whose course is influenced by configuration. However, instead of retaining the confusing *cis* and *trans* nomenclature for some of the trisubstituted olefins the author should have adopted the *E/Z* nomenclature. In Chapter 7 *S. R. Landor* informs in a lively manner about all the naturally occurring allenes so far isolated and about the successful and unsuccessful attempts at their synthesis. *A. Claesson* discusses the known biologically active allenes in Chapter 8 (93 references). In Chapter 9 entitled "Allenic Intermediates in Organic Synthesis", *A. Claesson* and *L.-J. Olsson* describe the reactions of stable and also unstable allenes only appearing as reaction intermediates, from the point of view of the type of compound synthesizable. Thematically this section would fit better into the second volume where a large proportion of the reactions are already described. Chapter 10, written by *W. Runge* and concerning spectroscopic properties, ought to be of great value to spectroscopically inclined synthetic chemists; here at last is a good collection of UV, IR, photoelectron, NMR and mass spectroscopic data, in contrast to books concerning spectroscopic methods in organic chemistry, where the allenes are usually shortchanged. In the last, very brief chapter *P. D. Landor* reports on the methods of synthesis of nine specialized, variously functionalized allenes; an expansion of this section would have been desirable.

This three volume monograph is very readable, because the text is copiously illustrated with structural formulas. The typesetting of the text and formulas is very good and, apart from a few unimportant exceptions that were perhaps unavoidable in a first edition, free from errors. The great value of this work is based on two facts: The individual sections are written by leading specialists and, for the first time, a complete picture is given of practically every aspect of allene chemistry. (The whole thing ought to have been published as one volume, which would undoubtedly have lowered the price.)

Even taking into account the small imperfections mentioned here, this monograph, consisting of three books can be warmly recommended to all who are concerned with or wish to be concerned with the chemistry of allenes and who require a comprehensive overview. The high price will certainly prevent many people from acquiring a personal copy; however, it ought to be available in departmental libraries to ensure its accessibility to undergraduates and graduate students alike. This work offers the specialist a solid basis, which covers all significant publications up to 1980 and from which he can research the literature of the last few years for himself. This is very necessary because we are at present in a phase of rapid development in the field of allene chemistry.

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Encyclopaedia of the Terpenoids. Vol. 1: A—H, Vol. 2: I—Z. By *J. S. Glasby*. John Wiley, Chichester 1982. 2646 pp., bound, £ 250.00.

The systematic coverage of the vast field of naturally occurring terpene derivatives is, without doubt, a very useful and urgent task, particularly since the work by *Devon* and *Scott* only covers the literature up to 1971. The present comprehensive summary unfortunately only covers the literature up to the end of 1979, but nevertheless includes more than 10000 compounds. It is, however, questionable whether all the substances included belong here, since substances such as thelepine, for example, are included although it can scarcely be described as a terpenoid. (Thelepine is 3′,5′,7-bromo-5-hydroxymethyl-2-spiro[benzofuran-2(3*H*),1′-cyclohexa-2′,5′-diene]-4′-one.) Furthermore, the indole alkaloids are also regarded as terpenoids, which is perhaps defensible on the grounds of their biogenesis from loganine, even though it does not seem very useful. Neither does the inclusion of substances whose structure is completely unknown seem to serve any useful purpose.

The formulas are very clearly presented and great care has been taken in the indication of stereochemistry. There

are literature references as well as spectroscopic and other data for each substance. The melting point and optical rotation are given in as far as they are available. The source plant from which the substance was isolated is also always reported. It would perhaps have been of value to have included the family as supplementary information.

The arrangement of the work is problematical. The decision was taken to list the compounds alphabetically without regard to their belonging to particular compound classes. This leads, on the one hand, to problems with the many terpenes that do not possess a trivial name and, on the other hand, makes it very difficult to search for a particular substance whose trivial name is unknown, in spite of the presence of a formula index. Since one often wishes to establish whether a certain compound is already known or not, classification according to substance type would have been very helpful.

It is only natural that a work of this magnitude should contain errors, as can be illustrated by a couple of accidentally found examples. Thujopsine and thujopsadiene lack ring three and yomogiartemine and δ-yohimbine both lack a carbon atom.

All in all this present work is a useful supplement to the somewhat out-of-date compilation of *Devon* and *Scott*. The very generous, but not very compact printing, unfortunately means that the price is relatively high, so that this "encyclopaedia" is only mainly intended for libraries.

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Enrichment Techniques for Inorganic Trace Analysis. By *A. Mizuike*. Springer-Verlag, Berlin 1983. viii, 144 pp., bound, DM 72.00.

Enrichment techniques in combination with powerful detection methods are extraordinarily important for the proper and sure analysis of trace elements. It is, therefore, praiseworthy that a book devoted to this theme has been included in the informative series "Introduction to chemical laboratory practice". Starting from the increasing importance of trace elements in science and technology and the, thereby, increasing demands on trace analysis, the author, who is professor of analytical chemistry at the University of Nagoya, provides a review of the principles and methods of chemical and physical enrichment techniques for trace components in materials in various states of aggregation.

The foundation-laying introductory chapters treat the general concepts such as yield, enrichment factors and, in particular, the most important sources of systematic errors, that is, contamination and loss of material. Sensible and practical suggestions are made for minimizing these errors, which are particularly important in ultra trace analysis.

The main portion of the book consists of the presentation of the fundamentals and application possibilities (studded with many important practical hints) of the most important "unit operations" for the enrichment of trace elements: Evaporation (from solutions, solids and molten salts), liquid-liquid extraction (in its many varieties), selective dissolution, precipitation reactions, electrochemical separation and dissolution, sorption, ion exchange and liquid chromatography, flotation, freezing-out and zone melting, filtration, centrifugation, particle removal from gases, gas separation.

Each basic operation is described in detail and its potentialities and limitations illustrated with examples. Apart from this, the author attempts to assist the reader with the solution of his own problems by including a large number of references (a total of 785 citations), many case descriptions, and individual exercises. Although this book is not a laboratory manual, I have no doubt of its usefulness for all workers confronted with practical problems in the enrichment of trace elements.

In summary, this book makes an excellent impression. It contains a wealth of information, is clearly written, comprehensive and interesting. It can be recommended without reservation not only to students and teachers but also to practical workers in the field of trace analysis.

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Chemistry and Biology of β-Lactam Antibiotics. Edited by *R. B. Morin* and *M. Gorman*. Academic Press, New York 1982. Vol. 1: Penicillins and Cephalosporins. xl, 453 pp., bound, $ 73.00; Vol. 2: Nontraditional β-Lactam Antibiotics. xii, 408 pp., bound, $ 64.00; Vol. 3: Biochemistry. xiv, 424 pp., bound, $ 64.00.

In 1982, ten years after the monograph "Cephalosporins and Penicillins" edited by *E. H. Flynn* and published in 1972, a new three volume work was published, which summarizes in about 1300 pages the enormous advances that have been made in the intervening period in the field of β-lactam antibiotics.

The work, which is dedicated to the memory of *R. B. Woodward*, begins with the personal reminiscences of *Abraham* on the developments in penicillins and in his main field of cephalosporins.

In the first volume *Cooper* and *Koppel* treat penicillin sulfoxides comprehensively, while *Kukolja* and *Chauvette* discuss modifications at the 3-position of cephalosporins, and *Gordon* and *Sykes* deal with the cephamycin antibiotics. *Webber* and *Wheeler* survey the antimicrobial and pharmacokinetic properties of the newer penicillins and cephalosporins, particularly those of the third generation. The first volume concludes with an interesting chapter by *Boyd* covering theoretical and physicochemical studies of β-lactam antibiotics.

In the second volume *Nagata, Narisada* and *Yoshida* discuss the partial synthesis of cephalosporin analogues with modified nuclei, particularly the synthesis of the highly biologically active 1-oxocephems. *Holden* describes progress in the total synthesis of penicillins, cephalosporins and their analogues with nuclear modifications. *Kamiya, Aoki* and *Mine* discuss the new monocyclic nocardicins which are active against gram-negative bacteria; their synthesis is also covered. *Ratcliffe* and *Albers-Schönberg* discuss the chemistry of the new thienamycins and other carbapenem antibiotics, while the penems, which were first studied intensively at the Woodward Institute in Basle, are discussed by *Ernest*. The second volume concludes with a review by *Cherry* and *Newall* of the chemistry and chemical modification of clavulanic acid, a highly active inhibi-

tor of β-lactamases which has a synergetic effect, e.g. in combination with ampicillin and cephaloridin.

In the third volume *Queener* and *Neuss* discuss the biosynthesis of β-lactam antibiotics; *Elander* and *Aoki* cover the β-lactam-producing microorganisms, while *Sykes* and *Bush* outline the physiology and biochemistry of β-lactamases and their deactivation, e.g. by clavulanic acid. *Waxman* and *Strominger* summarize present knowledge concerning biochemical mechanisms of the biological action of the β-lactam antibiotics, while *Kammer* attempts to cover the overwhelming importance of β-lactam antibiotics to present-day clinical medicine in only 13 pages. *Schockman, Daneo-Moore, McDowell* and *Wong* complete the third volume with a survey of the relationship between the inhibition of cell wall synthesis and the lethality towards bacteria.

Then follows a chapter by *Koster, Cimarusti* and *Sykes*, which evidently belongs to Volume 2, concerning the new monocyclic monobactams, which are largely resistant to β-lactamases and are often highly active against gram-negative bacteria.

An appendix lists all β-lactam antibiotics that are currently commercially available.

Finally, exact experimental details are given for the difficult and interesting introduction of the 7-methoxy group into cephalosporins, the total synthesis of amino-β-lactams, and the cell-free enzymatic conversion of penicillin N into cephalosporins.

The authors from many industrial organizations and several universities provide a very good survey of the whole field, the importance of which for the control of infectious diseases cannot be overestimated. These volumes are also a treasure chest for the nonspecialist—for everyone who, for example, is concerned with the total synthesis and modification of natural products, for the sulfur chemist (cf. the chapter by *Cooper* and *Koppel* on penicillin sulfoxides), or for biochemists and microbiologists. The volumes are carefully printed and bound and largely free from errors. Unfortunately the quality of reproduction of the numerous chemical formulas, which seem in part to have been provided by the authors and directly reproduced, is variable.

Taken as a whole the work is to be recommended to all natural product and sulfur chemists and, of course, all libraries should acquire it.

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Electron and Ion Microscopy and Microanalysis. By *L. E. Murr*, Marcel Dekker, Basel, 1982. xiv, 793 pp., bound, SFr. 185.00.

This book is an extension and revision by the author himself of his book "Electron Optical Applications in Material Science" published in 1970. The present work addresses two groups: First, university lecturers and advanced students who teach or take part in courses on electron and ion microscopy, electron and ion microscopical applications, or microanalysis. The presentation of all of the material would take up at least two semesters. A suggestion for distributing the material among individual lectures and laboratory demonstrations is given at the end of the book and offers a framework that can, if necessary, be supplemented.

The second group addressed consists of scientists and engineers in the various disciplines of materials science—physicists, chemists, metallurgists, ceramists—who wish to characterize materials by electron- and ion-microscopy. One of the major concerns of the author has been to create an awareness of the diversity of available investigation techniques, discussing their advantages and disadvantages, pointing out differences, and giving reasons for difficulties of interpretation.

The author describes all the relevant techniques that are known: conventional transmission electron microscopy at medium and high voltages, scanning transmission electron microscopy and scanning transmission ion microscopy, X-ray microscopy, emission microscopy using photo and field electron emission, and field ion microscopy. He compares the suitabilities of one-stage, two-stage and extraction replicas for the representation of surfaces with reflection electron microscopical imaging and the various methods of operating surface scanning electron microscopes or the information capabilities of electron mirror microscopes. He treats electron diffraction with slow and fast electrons, as well as channelling and Kikuchi diagrams. Just as complete is his discussion of microanalysis with electron, ion or atom probes: the spectroscopy of characteristic X-rays (both wavelength and energy-dispersive), Auger and photoelectrons, electron energy loss spectrometry and the mass spectrometry of scattered or secondary ions.

The basic theory is treated thoroughly and comprehensively, without becoming either too theoretical or too general; the immediate relevance to practice is always emphasized. Nevertheless, this is not simply a book concerned with the description of instruments; the methods of operation and the properties of the instruments and their components are described only so far as is necessary for judging their applicability to the solution of a particular problem. The text is supplemented by numerous electron micrographs from many areas of application and by many carefully thought-out and very clear drawings.

For a complete understanding of the bulk of the book, the reader should have a mathematical background equivalent to that required in engineering courses, including differential equations and matrix algebra.

At the end of each chapter the reader will find a number of exercises suitable for testing the level of understanding he has reached. This is particularly useful for those who wish to engage in private study. The exercises cover just those problems which confront the practitioner daily, so that everyone will enjoy working through them. The author provides solutions at the end of the book.

Each chapter contains a list of references cited in the text and, separately, suggestions for supplementary reading (the wide range of material, of course, precludes any possibility that the list is exhaustive).

An appendix deals with the basic theory of crystallography, which is necessary for the understanding of several sections and knowledge of which has been assumed. Also in the appendix there is a compilation of the most usual methods of sample preparation. The included computer programs for the analysis of diffraction diagrams and the tables of material data will be accepted as welcome aids by the practicing scientist and engineer.

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Analysis of Enzyme Structure and Activity by Protein Engineering**

By Alan R. Fersht*, Jian-Ping Shi, Anthony J. Wilkinson, David M. Blow, Paul Carter, Mary M. Y. Waye, and Greg P. Winter

Structure-activity relationships of enzymes can now be analyzed for the first time by the systematic alteration of protein structure. Recent developments in the chemical synthesis of DNA fragments and recombinant DNA technology enable the facile modification of proteins by highly specific mutagenesis of their genes. Kinetic analysis of the mutant enzymes combined with high-resolution structural data from protein X-ray crystallography allow direct measurements on the relationships between structure and function. In particular, the strength and nature of enzyme-substrate interactions and their detailed roles in catalysis and specificity can now be studied. We have developed such analysis of enzyme structure-function by site-directed mutagenesis of the tyrosyl-tRNA synthetase from *Bacillus stearothermophilus*, concentrating so far on the subtle role of hydrogen bonding in both substrate specificity and catalysis. We find that the energetics of tyrosine and ATP binding must be analyzed in terms of an exchange reaction with solvent water. Based on this idea and structural data, we have engineered an enzyme of improved enzyme-substrate affinity, and there thus appear to be real prospects of engineering proteins of new specificities, activities, and structural properties. We are also using protein engineering to gather direct information on the nature of enzyme catalysis. For example, we find the catalysis of formation of Tyr-AMP from Tyr and ATP is due largely to electrostatic and hydrogen bonding interactions that are stronger in the transition state than in the ground state—a "strain" mechanism rather than acid-base or covalent catalysis.

1. Introduction

The study of enzymes has been revolutionized by two major developments: knowledge of three-dimensional protein structure from X-ray protein crystallography and the ability to produce large quantities of sometimes otherwise inaccessible enzymes by genetic engineering. These methods are now being combined to produce enzymes having novel properties by the new discipline of "protein engineering".

Protein crystallography has provided, over the past twenty years, the necessary structural information for modifying enzymes, but the ability to change structure has been the stumbling block to producing new enzymes. Although there have been some isolated examples of synthesizing enzymes de novo by classical peptide synthesis, this procedure is too laborious and too limited to be of general use for producing novel enzymes. Further, synthetic proteins often do not fold into their native structures. The logical way to tackle the problem of protein synthesis is to copy nature and work at the level of DNA: DNA is the natural

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genetic material and can be used indefinitely to generate more supplies of protein; the simple rugged structure of DNA causes no problems of folding; DNA may be mutated and recombined in vitro to generate novel genes in a way analogous to the generation of new structures during evolution. This process of producing new activities by mutation of existing structures is how the problem of producing novel enzymes is presently being approached. Although it is not yet possible to design new enzymes ab initio, since the rules governing the folding of protein chains are not sufficiently well understood, it is possible to make variations on existing structural themes by controlled mutation of the gene encoding the relevant protein. In this article, we outline the results obtained from experiments on one particular enzyme and indicate the diversity and wealth of information that can be obtained on enzymes and enzymic catalysis.

2. Oligodeoxynucleotide-Directed Mutagenesis

The current method of generating specific mutations in DNA uses a chemically synthesized fragment of DNA that directs the mutation—oligodeoxynucleotide-directed mutagenesis. The mutator DNA fragment contains the codon (or its complementary codon) for the amino acid that is to replace the target amino residue in the native protein. The procedure was introduced in 1973[1]. The determination of the DNA sequence of a bacteriophage (ΦX174) by *Sanger*'s laboratory in 1976–1978[2] enabled the method to be put into practice. Oligodeoxynucleotide-directed mutagenesis was used in 1978 to create point mutations in bacteriophage ΦX174[3,4], and has subsequently been fashioned into a precision tool[5]. At the end of 1982, three papers were published reporting, for the first time, the site-directed mutagenesis of amino acid residues in the structural genes of enzymes of defined mechanism[6,7,8]. One of these examples involved an enzyme of known three-dimensional structure, the tyrosyl-tRNA synthetase from *Bacillus stearothermophilus*[6], and so it was possible to analyze the results in terms of structure and to initiate a systematic programme for dissecting the structure and activity of an enzyme.

The method of mutating amino acid residues in the tyrosyl-tRNA synthetase is illustrative[6,9] (Fig. 1). The gene coding for the enzyme was cloned into the bacteriophage vector M13 (this is a single-stranded DNA bacteriophage and is thus ideal for several of the following manipulations); a short oligodeoxynucleotide primer (12 to 20 residues) was synthesized that is complementary to the sequence of the DNA to be mutated, apart from a single mismatch; the mismatch was designed to convert the codon for the target amino acid into that for the desired mutant amino acid residue; the oligodeoxynucleotide was an-

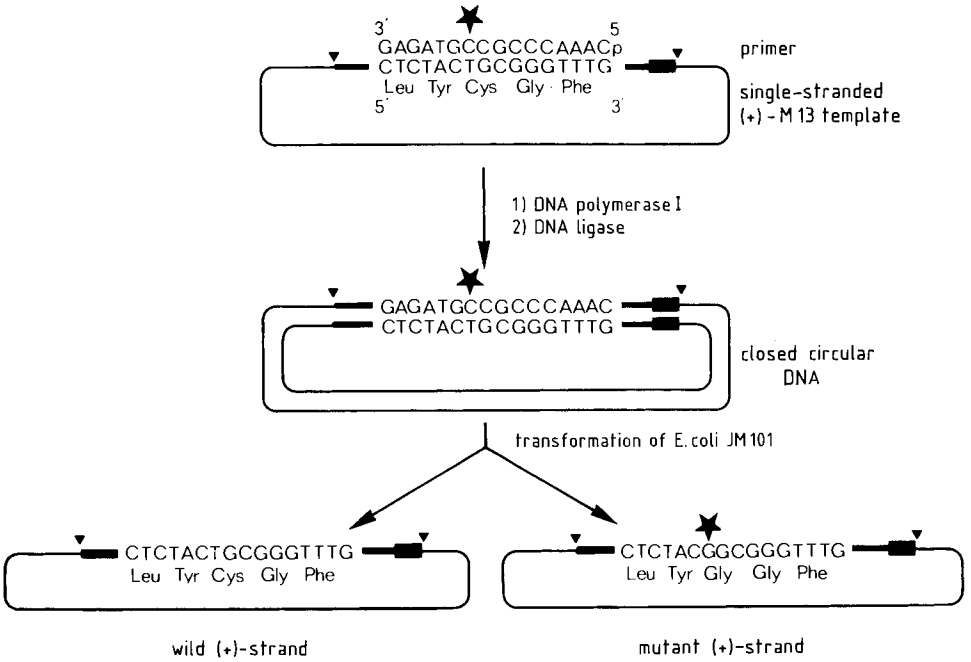


Fig. 1. Schematic representation of oligodeoxynucleotide-directed mutagenesis. The mismatched primer is designed to convert the codon for cysteine (TGC) into that for glycine (GGC). The gene for mutation must be obtained in the form of single-stranded DNA before the primer can be annealed. This was done for the tyrosyl-tRNA synthetase gene by subcloning it from the plasmid pBR322 into bacteriophage M13, a parasitic bacteriophage that does not destroy its host. ▼ Indicates the limits of the insert; the thickened line indicates the *B. stearothermophilus* DNA; ■, the portion of pBR322. The genome of this filamentous bacteriophage is a covalent circle of single-stranded DNA that becomes a covalent double-stranded circle (termed RF) during its replication in *E. coli*. The subcloning is performed on the double-stranded form, and the mutation on the single-stranded. A mutant gene is formed by copying the DNA of the bacteriophage and cloned gene from the 3′ end of the mismatched primer using DNA polymerase and ligating to the 5′ end with DNA ligase. The resultant heteroduplex is introduced into *E. coli* (strain JM101 in this case) to yield clones of cells; some contain the bacteriophage with the gene for the wild-type enzyme, others the gene for the mutant. The clones may be screened as described in the text. The clones produce large quantities of tyrosyl-tRNA synthetase. For further details see [6, 9].

nealed to the single-stranded DNA and used as a primer for replication catalyzed by a DNA polymerase; the new strand was ligated using DNA ligase to produce a heteroduplex of wild-type and mutant DNA; host cells of *Escherichia coli* were transformed by the heteroduplex to give clones containing mutant or wild-type vector. Mutant clones were identified using the ^{32}P-labeled mutagenic primer as a probe in a hybridization assay, since it binds preferentially to the mutant DNA[10]. The frequency of mutants varies from 1 to 50%. Mutant enzymes are produced in high yield from the clones.

Oligodeoxynucleotide mutagenesis has been extended to make deletions and insertions of sequences. For example, a mutator DNA fragment containing an additional codon somewhere in its middle anneals to the target with the three additional bases looping out. After replication, the synthetic strand contains the extra codon. Conversely, a longer primer, e.g. a 24-mer, may be synthesized in which the first 12 residues are complementary to one region of the gene and the other 12 to a distal region. On annealing the primer to the gene, the intervening section of the gene is looped out. After replication, the synthetic strand lacks the looped-out section. There are also more sophisticated methods of causing deletions[11].

3. The Tyrosyl-tRNA Synthetase from *B. stearothermophilus*

The enzyme studied most extensively so far by oligodeoxynucleotide-directed mutagenesis is the tyrosyl-tRNA synthetase (TyrTS)[*] from *B. stearothermophilus*. To date, we have prepared and analyzed some 20 mutants involving single mutations, double mutations, and extensive deletions.

This enzyme catalyzes the aminoacylation of $tRNA^{Tyr}$ in a two-step reaction [eqs. (a) and (b)][12].

$$E + Tyr + ATP \longrightarrow E\cdot Tyr\text{-}AMP + PP_i \quad (a)$$

$$E\cdot Tyr\text{-}AMP + tRNA^{Tyr} \longrightarrow Tyr\text{-}tRNA^{Tyr} + AMP + E \quad (b)$$

It is a symmetrical dimer of $M_r = 2 \times 47\,500$[13,14]. The nucleotide sequence of the gene has been determined from a clone in the vector pBR322[15]. X-ray crystallographic studies on the enzyme at 0.3 nm resolution have been published (Fig. 2)[16a], and in subsequent work refinement has been extended to a nominal 0.21 nm[16b]. Most importantly, the crystal structure of the enzyme-bound tyrosyl-adenylate complex has also been solved[17] so that there is the rare opportunity of direct knowledge of the interactions of the enzyme with a substrate (Fig. 3).

Aside from this, the tyrosyl-tRNA synthetase has convenient kinetic properties that render it a suitable target for mutagenesis studies: the enzyme is readily assayed by active-site titration, and hence accurate and reproducible steady-state kinetic measurements may be made[18]; the partial reaction of activation [eq. (a)] and the overall charging reaction are readily determined by straightforward assays; the pre-steady state kinetics of activation may be followed by stopped-flow fluorescence studies[19] and those of the transfer step [eq. (b)] by rapid quenching methods[12]. The enzyme also has interesting properties since it is a dimer. Kinetic studies show that the two active sites interact so that in solution[20] only one tyrosine as well as one $tRNA^{Tyr}$[21,22] and one tyrosyl adenylate are bound tightly per two active sites[23].

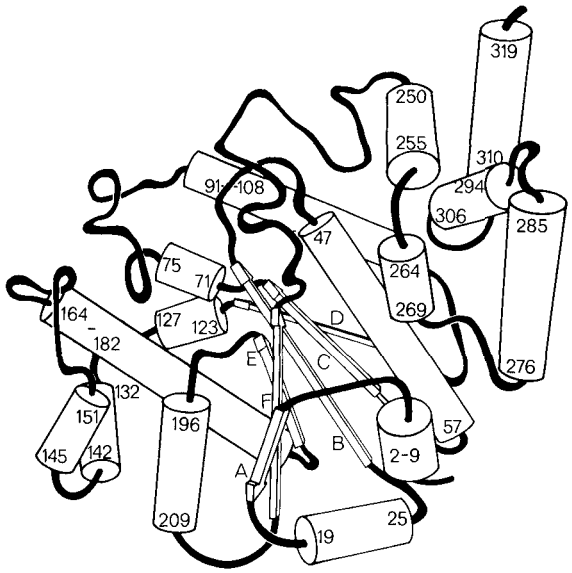


Fig. 2. Crystal structure of one of the symmetrical subunits of the tyrosyl-tRNA synthetase. Note that the tyrosyl adenylate (see Figs. 3 and 4) makes hydrogen bonds with side chains from the helices spanning residues 47–57 and 164–182, and the strand of β-sheet B.

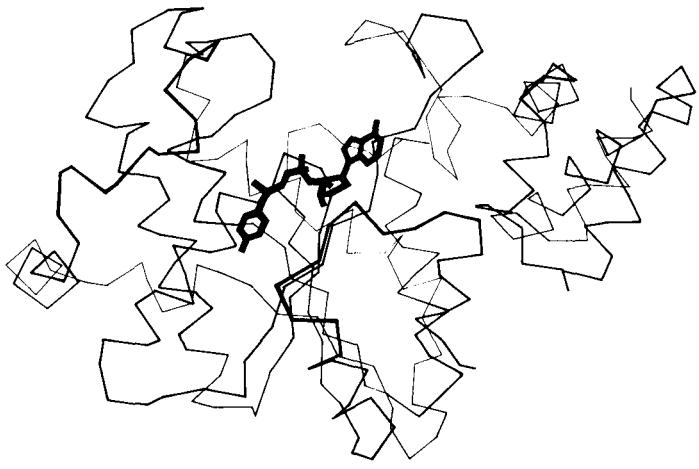


Fig. 3. Tyrosyl-tRNA synthetase forms a stable, enzyme-bound tyrosyl adenylate complex. On addition of tyrosine and ATP to the crystals of the enzyme, they first crack and then reanneal to produce the intermediate which is stable in the absence of tRNA or high concentrations of pyrophosphate. The sketch shows the backbone of the enzyme and the bound substrate which were determined directly by X-ray diffraction studies.

The tyrosyl-tRNA synthetase from *B. stearothermophilus*—a thermophilic organism—has one further very important property: the enzyme is thermostable and loses no activity on prolonged incubation at 56 °C, unlike the enzyme from *Escherichia coli* which is rapidly denatured. As the mutant tyrosyl-tRNA synthetases used in the studies

[*] Abbreviations: TyrTS = tyrosyl-tRNS synthetase; mutants are indicated thus: TyrTS(Cys35-Ser35) = TyrTS containing the mutation Cys-35 to Ser-35; k_{cat} and K_M are the catalytic and Michaelis constants, respectively, in the Michaelis-Menten equation.

are produced from the clones in *E. coli*, provided the mutation does not reduce thermostability, any background native enzyme from *E. coli* can be readily removed by heating. Thus, weakly active mutants may be studied without interference from active native enzyme.

4. Strategy for Studying Structure-Activity Relationships

The utilization of binding energy is at the heart of enzyme catalysis and specificity. There is a simple equation relating the rate constant k_{cat}/K_M of the Michaelis-Menten equation to the binding energy of the enzyme and substrate[24,25] [eq. (c)]

$$RT\ln(k_{cat}/K_M) = RT\ln(kT/h) - \Delta G^{+} - \Delta G_s \qquad (c)$$

where ΔG_s is the binding energy between the enzyme and substrate, ΔG^{+} is the energy of activation, and k and h are the Boltzmann and Planck constants, respectively.

Using site-directed mutagenesis, we are able to alter the binding energy term ΔG_s by changing the side chains of the amino acid residues that interact with the substrate. The changes in binding energy may be calculated from k_{cat}/K_M using eq. (c) and the importance of the interaction evaluated. This provides an experimental means of measuring ΔG_s for the interactions. Theoretical considerations[24,25] show that reaction rate is optimized when the binding energies of these interactions are realized in the enzyme-transition state complex rather than the enzyme-substrate complex—the concept of transition-state stabilization. Furthermore, hydrogen bonds should be particularly important in mediating such differential binding effects because the strength of hydrogen bonding varies strongly with interatomic distance and hence is sensitive to the movement of atoms during the reaction. Accordingly, the initial strategy of our experiments was to alter residues that form hydrogen bonds with the substrates.

5. Nature of Hydrogen Bonding of Enzymes with Substrates

The mutation of Cys-35 to Ser-35 in tyrosine-tRNA synthetase was the very first experiment in which a residue at the active site of an enzyme of known three-dimensional structure was specifically mutated by protein engineering, leading to an enzyme of altered activity[6]. As shown in Figure 4, Cys-35 forms a hydrogen bond with the 3′-hydroxyl of the ribose moiety of Tyr-AMP. The mutation experiment changes −SH to −OH in the amino acid side chain. Although the *absolute* strength of the hydrogen bond −OH···O− is greater than that of −SH···O− in simple intermolecular associations, it is found on comparing the wild-type TyrTS with the mutant TyrTS(Cys35-Ser35) (Table 1) that the former enzyme has a higher affinity (1.2 kcal mol^{-1}) for the ATP substrate [calculated from eq. (c)]. There are two reasons for this:

1) It is not the absolute strength of a hydrogen bond in an enzyme-substrate complex that affects the enzyme-substrate dissociation constant that is important; rather it is

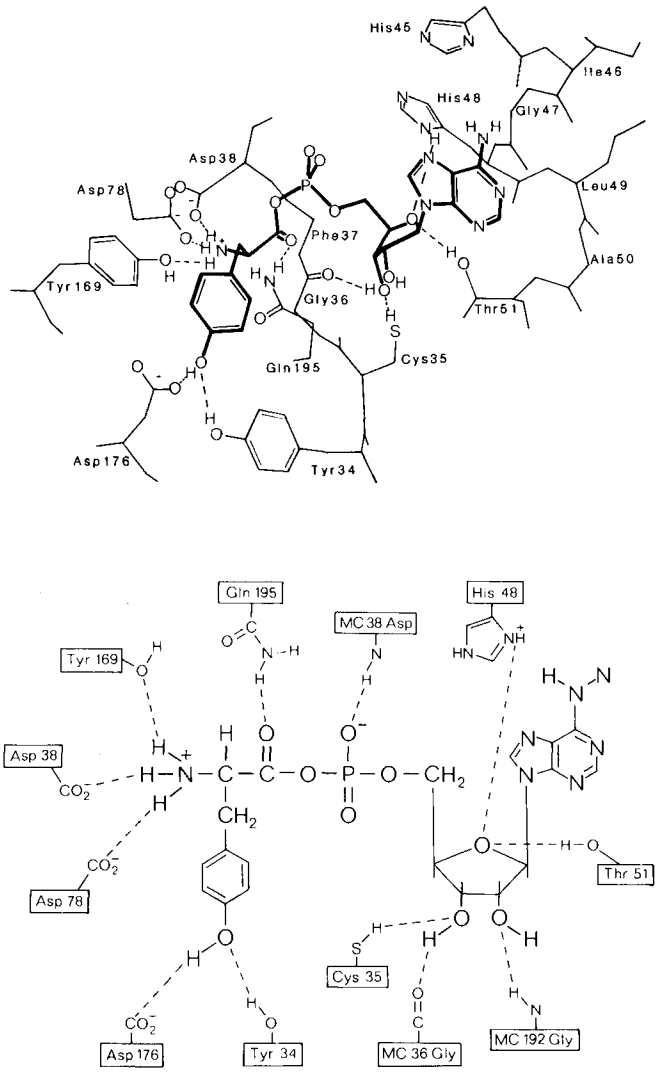


Fig. 4. Active site of the tyrosyl-tRNA synthetase with the bound tyrosyl adenylate. Top: an expanded and more detailed view of Figure 3. Bottom: schematic sketch of residues that probably form hydrogen bonds. These interactions are tentative at the resolution of the structure, but most have now been confirmed by site-directed mutagenesis.

Table 1. Activation of tyrosine by TyrTS-wild type and mutants at 25°C (details see [9]).

Enzyme	k_{cut} [s^{-1}]	K_M (ATP) [mM]	K_M (Tyr) [μM]	k_{cat}/K_M (ATP) [$s^{-1}\,M^{-1}$]
TyrTS	7.6	0.9	2.4	8400
TyrTS(Cys35-Gly35)	2.8	2.6	2.7	1120
TyrTS(Cys35-Ser35)	2.4	2.4	2.6	1000

the *difference* in energies of the hydrogen bond donor/acceptor in the free enzyme and the acceptor/donor in the free substrate when they are separately hydrogen-bonded to solvent water relative to the situation when they are hydrogen-bonded to each other [eq. (d)]:

$$E\cdots OH_2 + S\cdots HOH \longrightarrow E\cdots S + HOH\cdots OH_2 \qquad (d)$$

2) There are geometrical constraints on hydrogen-bond formation in enzyme-substrate complexes because the donor and acceptor groups are held at fixed distances from each other. For example, the S–O distance in SH···O

bonds is 0.5 nm longer than the O–O in OH···O. The substitution of the side-chain hydroxy group of a serine for a cysteine residue is thus energetically unfavorable because the O–O distance is too long in a rigid active site[9]. Comparison of TyrTS(Cys35-Ser35) and another mutant in which the side chain has been completely removed, TyrTS(Cys35-Gly35) (Table 1), shows that the serine side chain contributes no apparent binding energy with the substrate and, if anything, the presence of the side chain actually weakens binding.

It is concluded that the presence of a poor (too long) hydrogen bond in an enzyme-substrate complex can increase the dissociation constant and the value of k_{cat}/K_M. Perhaps the removal of a weak hydrogen bond by site-directed mutagenesis could be used to increase the affinity of an enzyme for its substrate.

6. Improving the Affinity of the Enzyme for ATP

Preliminary crystallographic studies indicated that Thr-51 makes a long hydrogen bond with the tyrosyl adenylate (Fig. 4). Furthermore, although all the other side chains illustrated in Figure 4 are conserved in the *E. coli* enzyme, it has a proline residue in this position that cannot possibly make a hydrogen bond with the substrate and will also distort the secondary structure in this region. Accordingly, in the light of the conclusion of the last section, we changed Thr-51 first to Ala-51 to determine the effect of deleting the hydrogen bond, and then to Pro-51 to examine the results of causing a larger structural change[26].

Table 2. Increase in affinity for ATP in tyrosine activation by TyrTs upon mutation of Thr-51. Reaction at 25 °C (details see [26]).

Enzyme	k_{cat} [s^{-1}]	K_M (ATP) [mM]	K_M (Tyr) [μM]	k_{cat}/K_M (ATP) [s^{-1} M^{-1}]
TyrTS	7.6	0.9	2.4	8400
TyrTS(Thr51-Ala51)	8.6	0.54	2.0	15900
TyrTS(Thr51-Pro51)	12.0	0.058	—	208000

The results for activation of tyrosine by these mutants are listed in Table 2. It is seen that the K_M for ATP of TyrTS(Thr51-Ala51) is two times lower than that of the wild type. It appears, in fact, that the interaction of threonine with the substrate is very weak and hence lowers the affinity of the enzyme for the substrate. Site-directed mutagenesis is thus a good fine-structure probe for hydrogen bonding.

Mutation of the wild type to TyrTS(Thr51-Pro51) causes a massive increase in the value of k_{cat}/K_M, involving both an increase in k_{cat} and a decrease in K_M (for ATP). Thus, engineering a single point-mutation has caused a significant improvement in enzymic activity and, hence, shows that there are real biotechnological possibilities of engineering the activities of enzymes in vitro.

What is the reason for this dramatic improvement in affinity of the enzyme for ATP? Thr-51 is located in an α-helix (amino acid residues 47–57) (Fig. 2), and the introduction of a proline would be expected to distort the helix structure between residues 47–50. The improved affinity

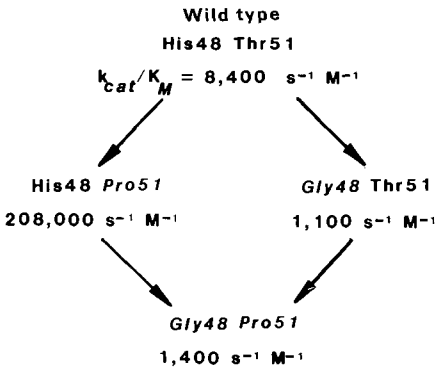
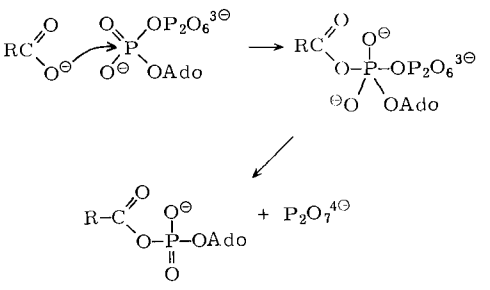


Fig. 5. Use of double mutants for investigating structural changes. (Mutated residues are shown in italics.) The high value of k_{cat}/K_M for the mutant TyrTS(Thr51-Pro51) requires the presence of both His48 *and* Pro51. If His48 is first converted into Gly48 (right), mutation of Thr51 to Pro51 to generate the double mutant TyrTS(His48-Gly48, Thr51-Pro51) at the bottom leads to little increase in the rate constant.

might thus result from a new contact formed between enzyme and substrate, from an improved interaction at an existing contact, or from a direct interaction of the substrate and the pyrrolidine ring of the proline. An earlier mutagenesis experiment had shown that His-48 forms an H-bond to ATP which only gains 1.2 kcal mol^{-1}. We were therefore interested whether the effect of proline was to distort the polypeptide backbone and thereby improve the interaction of His-48 with the substrate. To prove this, we constructed a double mutant TyrTS(His48,Thr51-Gly48,Pro51). This mutant has approximately the same activity as the TyrTS(His48-Gly48) mutant, indicating that the effect of Thr-51 is mediated via the imidazole group of His-48 (Fig. 4). From the cycle shown in Figure 5, we can calculate, using equation (c), that the imidazole group of His-48 contributes 1.2 kcal mol^{-1} to binding energy in the wild-type enzyme and 3 kcal mol^{-1} in the Pro-51 mutant. This result shows how a second mutation introduced into the active site of an enzyme can be used as a probe of the structural change introduced by the first mutation.

7. Evidence for Transition-State Stabilization in the Activation Reaction

How is the attack of the tyrosyl carboxy group on ATP [eq. (a)] catalyzed? This reaction involves an associative in-line displacement of pyrophosphate from ATP [eq. (e)][27].



(e)

General base-catalysis of the nucleophilic attack is not possible since the carboxylate is fully ionized. Nucleophilic catalysis by a group on the enzyme forming an inter-

mediate with AMP is unlikely since ATP is already an "activated" compound containing a good leaving group (pyrophosphate). The remaining possibilities are electrostatic catalysis and transition state stabilization, whereby certain groups on the enzyme make stronger interactions with the substrate transition state. For transition state stabilization it is predicted that when a group on the enzyme is removed, as in a site-directed mutagenesis experiment, the affinity of the enzyme for the substrate will be decreased to some extent, but the affinity for the transition state will be decreased to a much greater extent than if the transition state had been stabilized. This means that the value of K_M may be increased to a greater or lesser extent but the value of k_{cat} will fall, as shown in Table 3. Particularly noteworthy is the change from His-45 to Asn-45 leading to a 2000-fold drop in k_{cat}, whilst the values of K_M are hardly affected (*J.-P. Shi*, unpublished). Similarly, the rate of attack of pyrophosphate on the tyrosyl adenylate complex is lowered 2000-fold in TyrTS(Hys45-Asn45) (unpublished data). His-45 does not interact with the tyrosyl adenylate in the crystal structure (Fig. 4). Model building studies by Dr. *R. J. Leatherbarrow* (unpublished) show that the γ-phosphoryl group of the pentacovalent intermediate in eq. (e) can make a hydrogen bond with His-45[*].

Table 3. Influence of various mutations on the activation of tyrosine.

Mutant	k_{cat} [s^{-1}]	K_M (ATP) [mM]	k_{cat}/K_M [s^{-1} M^{-1}]
TyrTS [a]	7.6	0.9	8400
TyrTS(cys35-Gly35) [a]	2.8	2.6	1120
TyrTS(Cys35-Ser35) [a]	2.4	2.4	1000
TyrTS(His48-Gly48) [b]	1.6	1.4	1140
TyrTS(His45-Asn45) [b]	0.003	1.0	3
TyrTS(Gln195-Gly195) [b]	0.16	2.5	64

[a] Ref. [9]. [b] Unpublished results.

Geometrical changes that occur during the activation reaction may be inferred from some of the mutations in hydrogen-bonding groups we have engineered based on the following reasoning. If an amino acid residue on the enzyme hydrogen bonds with the substrate equally well in the enzyme-transition state complex as in the enzyme-substrate complex, removal of that residue will affect only K_M and not k_{cat} (see [25] pp. 244–247). Similarly, removal of a residue that hydrogen bonds better in the enzyme-transition state complex will lower k_{cat}. We have found that k_{cat} for the activation reaction is sensitive to all changes made so far in residues that hydrogen-bond with ATP. Conversely, k_{cat} is insensitive to changing a residue that forms a hydrogen bond with the tyrosine hydroxy group (Tyr-34 to Phe-34 in Figure 4, (unpublished)). This suggests that during the activation reaction the bound tyrosine side-chain may move relatively little, but that the bound ATP moves towards the tyrosine carboxy as it makes a nucleophilic attack on the α-phosphoryl group of ATP. Since the strength of the hydrogen bonding of the enzyme with ATP increases as the transition state is reached, the enzyme must presumably be compressing the ATP and the tyrosine together.

[*] As indicated in Table 3, changes in k_{cat} and K_M may also arise from mechanisms such as "induced fit" and "non-productive binding". Because of this, the results of previous kinetic studies on structure-reactivity relationships from studies where the structure of the substrate has been altered have usually failed to provide unambiguous evidence for "strain" mechanisms (transition-state stabilization) [21]. However, the changes induced by site-directed mutagenesis of the tyrosyl-tRNA synthetase are more amenable for producing unambiguous analysis for the following reasons: 1) It will be possible to solve the structures of the native enzyme and enzyme-substrate complexes for the mutants by X-ray crystallography. 2) Many of the structural changes will be sufficiently small that the binding energetics may be calculated. Even in the absence of precise structural data, the combination of chemical intuition and inspection of the enzyme structure by computer graphics strongly suggests that transition-state stabilization by electrostatics and hydrogen bonding is operating.

8. Optimization of the Rate of Enzymic Reactions during Evolution

Various proposals have been made as to how enzymic rate constants should respond to selective pressure in evolution to maximize the overall rate of reaction[20,21,28]. One way of testing the validity of these models is by site-directed mutagenesis. Although the mutants we have generated are not necessarily the evolutionary precursors of the present native enzyme, they are possible forms of the enzyme that have been rejected during evolution, since the rate of spontaneous mutation is sufficiently high for them to have arisen and hence been tested. One simple theory for the effects of selective pressure on the evolution of maximum rate[20,21] predicts 1) that the catalytic term k_{cat}/K_M tends to a maximum (this is the consequence of the enzyme being complementary to the transition-state structure of the substrate) and 2) that values of k_{cat} and K_M tend to increase in parallel so that the value of K_M lies above the normal concentration of the substrate encountered in vivo. The net result is that the term $[S]_p k_{cat}/(K_M+[S]_p)$ is maximized in eq. (f), which gives the rate in vivo, where $[S]_p$ is the concentration of substrate in vivo. This is achieved by low-

$$v\ (\text{in vivo}) = [E]_0[S]_p k_{cat}/(K_M+[S]_p) \qquad (f)$$

ering the complementarity of the enzyme with the substrate in its unreacted structure while maintaining complementarity with the transition-state structure. Experimentally, the value of K_M for ATP in the aminoacylation reaction of native enzyme is 2.5 mM, a value close to the 2–3 mM found for the concentration of ATP found in vivo for many organisms. The full intrinsic binding energy of ATP and a protein is clearly not utilized here—the K_M for ATP and myosin is 10^{-13} M, for example[29]. In general, the values of k_{cat}/K_M for the mutants are lower than that for wild-type. The notable exception is the mutant TyrTS(Thr51-Pro51), where k_{cat}/K_M for the mutant is much higher (Table 4). However, the high value for k_{cat}/K_M is achieved by compensation of a low value of k_{cat} by a very low value of K_M for ATP. At physiological concentrations of ATP (2–3 mM), the native enzyme is more active than the mutant (as calculated by substituting the experimental values of k_{cat}, K_M, and [ATP] into eq. (f)). At lower concentrations of ATP, however, the mutant TyrTS(Thr51-Pro51) is more active. This illustrates the importance of enzymes maximizing their rate by adjusting their K_M values to the concen-

Table 4. Kinetics of the aminoacylation of tRNA [a].

Enzyme	Different ATP conc.			[ATP] [mM]		
	k_{cat} [s^{-1}]	K_M [mM]	k_{cat}/K_M [$s^{-1}M^{-1}$]	2.5[b]	0.25	0.025
				v [s^{-1}]		
TyrTS [c]	4.7	2.5	1860	2.35	0.43	0.05
TyrTS(Thr51-Pro51)[c]	1.8	0.019	95800	1.79	1.67	1.02
TyrTS(Thr51-Ala51)[c]	4.0	1.251	3200	2.7	0.67	0.078
TyrTS(Cys35-Gly35)[d]	1.9	6.1	320	0.55	0.075	0.008
TyrTS(Cys35-Ser35)[d]	1.3	6.4	200	0.36	0.049	0.005
TyrTS(His48-Gly48)[e]	2.4	8.7	278	0.54	0.067	0.047
TyrTS(Gln195-Gly195)[e]	0.15	6.2	24	0.043	0.006	0.0007

[a] Rate of aminoacylation of tRNA at 25°C [mol Tyr-tRNA · mol^{-1} enzyme · s^{-1}]. k_{cat} and K_M are rounded off, but k_{cat}/K_M is calculated from the exact values. [b] Approx. concentration in vivo. [c] Ref. [26]. [d] Ref. [9]. [e] Unpublished results.

trations of substrates in vivo. One other mutant TyrTS(Thr51-Ala51) has similar activity to the native enzyme at 25°C in vitro.

9. Structural Organization of the Tyrosyl-tRNA Synthetase

The crystal structure of the enzyme consists of a well-ordered *N*-terminal domain comprising residues 1—319 that binds tyrosyl adenylate, while the remaining 100 residues of the *C*-terminus are disordered[16]. The fragment of gene coding for the *N*-terminal domain has been prepared by a gene-deletion procedure, and the truncated protein isolated[11]. The truncated enzyme is fully active in the activation reaction [eq. (a)], but does not catalyze the transfer of tyrosine to tRNA or bind Tyr-tRNA. The structural division of the tyrosyl-tRNA synthetase is thus also a functional one in which an *N*-terminal domain is responsible for amino acid activation and a *C*-terminal domain for tRNA binding. A series of more general mutational experiments on the alanyl-tRNA synthetase, an enzyme of unknown three-dimensional structure, shows that this protein also has distinct regions for activation and transfer reactions[30].

10. Summary and Outlook

Although we know from personal communications from our colleagues that many other enzymes are now being studied by oligodeoxynucleotide-directed mutagenesis, there is little published work at present relating changes in activity to changes in structure. The work on β-lactamase[7,8] cannot be extended at present because the three-dimensional structure of the enzyme is not known; however, crystallographic work is in progress. Three mutants of dihydrofolate reductase have been prepared[31], and further work is in progress by other groups. However, we anticipate that in the next year or two there will be a plethora of exciting data published.

Protein engineering appears to be the answer to an enzymologist's prayer. The prospects are quite open-ended. At the purely academic level, the relationship between structure and activity of enzymes is now being analyzed directly: in the most basic experiments, groups directly involved in catalysis are being identified; in more sophisticated experiments, the role of enzyme-substrate interactions in catalysis and specificity is being studied. Future experiments will explore long-range effects of structural changes on activity and the transmission of the effects of substrate and effector binding through protein subunits. Experiments are being planned in various laboratories to change the thermostability of enzymes and to learn the structural basis of enzyme stability. Undoubtedly, protein engineering will be used to study enzyme folding. At the commercial level, protein engineering will be used to alter the physical properties of enzymes, such as their thermostability, solubility, pH optima etc., and hence optimize their use in biotechnological processes in vitro. Protein engineering will also be used to alter kinetic properties, such as the values of k_{cat} and K_M for substrates, and to change even the specificities of enzymes. The ultimate goal is to design tailor-made enzymes for every reaction.

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Organolanthanoid Compounds**

By Herbert Schumann*

Up to little more than a decade ago organolanthanoid compounds were still a curiosity. Apart from the description of an isolated number of cyclopentadienyl and indenyl derivatives, very few significant contributions had been made to this interesting sector of organometallic chemistry. However, subsequent systematic studies using modern preparative and analytical techniques, together with X-ray single crystal structure determinations, enabled the isolation and characterization of a large number of very interesting homoleptic and heteroleptic compounds in which the lanthanoid is bound to hydrogen, to substituted or unsubstituted cyclopentadienyl groups, to allyl or alkynyl groups, or even to phosphorus ylides, trimethylsilyl, and carbonylmetal groups. These compounds, which are all extremely sensitive to oxygen and water, open up new possibilities in the field of catalysis and have great potential in organic synthesis—as recent studies with pentamethylcyclopentadienyl derivatives, organolanthanoid(II) compounds, and hexamethyllanthanoid complexes have already shown.

1. Introduction

"Those elements whose valence electrons possess the same principal quantum number yield typical alkylelement compounds; all other elements which do not comply with this condition are not able to form such compounds". With this statement, which he made in 1926, *Aristid von Grosse* contested the ability of the transition metals as well as the lanthanoids to form stable organometallic compounds[1].

This postulate was based on the knowledge that a main group element forms stable compounds if its valence shell, consisting of s and p orbitals and covering completely occupied inner shells, acquires a total of eight electrons. To achieve such a stable noble-gas configuration, the transition metals require 18 electrons, while the lanthanoids and actinoids require as many as 32 electrons of different principal quantum numbers. Hence, all compounds which do not fulfill this requirement are unstable to a greater or less extent, but, at the same time, highly chemically reactive. The first example of a transition metal-to-carbon σ bond was demonstrated in an organotitanium compound in 1952[2].

The first indication of the existence of organolanthanoid compounds was furnished by the observation that methyl radicals react with lanthanum[3]. The reputed synthesis of triethylscandium and triethylyttrium, the first alkyl derivatives of the "rare earth metals", however, proved to be erroneous[4]. All the attempts made by *Gilman* et al. to prepare the first phenyllanthanum derivative, in connection with the separation of ^{235}U from ^{238}U via volatile uranium compounds, also met without success. Both the reaction of lanthanum trichloride with phenyllithium as well as that of lanthanum with diphenylmercury furnished only biphenyl[5].

The major breakthrough in organo-transition metal chemistry followed the discovery of ferrocene and other sandwich complexes in the second half of the 20th century. For instance, in their search for π-complexes of the lanthanoids in 1954, *Wilkinson* and *Birmingham* were able to synthesize the first tricyclopentadienyl derivatives of scandium, of yttrium, and of almost all of the other lanthanoids[6]. Fourteen years later, the first indenyl derivatives[7] and, in 1969, the first cyclooctatetraene complexes were described[8]. There then followed, in 1968/1970, the synthesis of triphenylscandium[9] and of lithium tetraphenyllanthanate(III) and praseodymate(III), the first homoleptic compounds of the lanthanoids[10]. However, it was not until the late seventies that these compounds became known on a broad front. Nowadays, numerous teams of chemists all around the world are engaged in studies relating to these new compounds and their fascinating properties.

The present article reviews two important aspects of this area of chemistry: 1) The methods which have proven most successful for the preparation of organolanthanoid compounds, and 2) the molecular structures of these compounds. For completeness, the derivatives of scandium and yttrium are also taken into consideration. Finally, the increasing importance of these compounds in preparative organic chemistry is outlined.—A number of review articles covering this field of chemistry have been published in recent years. Three of them, which reflect the latest state of research in more detail than is possible here, should be given special mention[11-13].

2. Organometallic Compounds with Lanthanoids in the Oxidation State +3

2.1. Tricyclopentadienyllanthanoid Compounds

The tricyclopentadienyl complexes of the lanthanoids were the first organometallic compounds of these "inner"

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[**] In this review article the types of compounds have been numbered systematically; lower case letters after the numbers signify the respective metal that is present: **a** stands for Sc, **b** for Y, **c** for La, ... **r** for Lu (see, e.g., Table 1). Ln signifies Sc, Y, La—Lu. Cp means cyclopentadienyl, as well as with substituents.

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transition elements to be prepared and have remained, until this day, the most intensively investigated derivatives. They are best prepared by the reaction of sodium cyclopentadienide **1** or potassium cyclopentadienide **2** with anhydrous lanthanoid trichlorides **3** in tetrahydrofuran (THF) under an inert gas[6,14]. The pure, THF-free compounds, $(C_5H_5)_3Ln$ **4**, are isolated by sublimation of the crude products in a high vacuum at temperatures above 200°C. Only in the case of the thermally sensitive $(C_5H_5)_3Eu$ **4i** are difficulties encountered with the removal of THF. These difficulties can, however, be overcome, either by using benzene as solvent[14] or, as could be shown in the preparation of **4i** from $C_5H_5EuCl_2\cdot(THF)_3$ **5i** and **1** in THF, by taking special care during the removal of THF[15]. The synthesis of the radioactive species $(C_5H_5)_3Pm$ **4g** was accomplished by reaction of $PmCl_3$ **3g** with molten $(C_5H_5)_2Be$ or $(C_5H_5)_2Mg$[16,17]. Compound **4g** had already been detected in 1967 in the matrix of $(C_5H_5)_3Nd$ **4f** after bombardment with neutrons[18].

$$\underset{\mathbf{3}}{LnCl_3} + 3\,\underset{\mathbf{1}}{C_5H_5Na} \xrightarrow{THF} \underset{\mathbf{4}}{(C_5H_5)_3Ln} + 3\,NaCl$$

Ln = Sc (**4a**), Y (**4b**), La (**4c**), Ce (**4d**), Pr (**4e**), Nd (**4f**), Sm (**4h**), Gd (**4k**), Tb (**4l**), Dy (**4m**), Ho (**4n**), Er (**4o**), Tm (**4p**), Yb (**4q**), Lu (**4r**).

$$2\,\underset{\mathbf{3g}}{PmCl_3} + 3(C_5H_5)_2M \longrightarrow \underset{\mathbf{4g}}{2(C_5H_5)_3Pm} + 3\,MCl_2$$

M = Be, Mg

Table 1. Physical properties of tricyclopentadienyllanthanoid compounds **4**.

$(C_5H_5)_3Ln$ **4** Ln		Color	M.p. [°C]	μ_{eff} [B. M.]	Ref.
Sc	**4a**	yellowish	240	[a]	[6]
Y	**4b**	yellowish	295	[a]	[6]
La	**4c**	colorless	395	[a]	[6]
Ce	**4d**	orange	435	2.46	[6]
Pr	**4e**	greenish	415	3.61	[6]
Nd	**4f**	blue	380	3.62	[6]
Pm	**4g**	yellow-orange			[17]
Sm	**4h**	orange	365	1.54	[6]
Eu	**4i**	brown			[15]
Gd	**4k**	yellowish	350	7.98	[6]
Tb	**4l**	colorless	316	8.9	[14]
Dy	**4m**	yellow	302	10.0	[6]
Ho	**4n**	yellow	295	10.2	[14]
Er	**4o**	pink	285	9.44	[6]
Tm	**4p**	yellow-green	278	7.1	[14]
Yb	**4q**	dark green	273	4.00	[6]
Lu	**4r**	colorless	264	[a]	[14]

[a] Diamagnetic.

All compounds **4** are air- and moisture-sensitive. Their colors, melting points, and magnetic moments are summarized in Table 1. Various spectroscopic investigations suggest strong ionic bonding between the lanthanoids in the oxidation state +3 and the negatively charged cyclopentadienyl ligands[19]. X-ray structure analyses of solvent-free **4a**[20] and **4h**[21] revealed the presence of chains in which di(η^5-cyclopentadienyl)lanthanoid units are bridged by the remaining C_5H_5 ligands, which, in turn, are η^5-bound to one lanthanoid atom and η^1-bound to the next. $(CH_3C_5H_4)_3Nd$ **6f** is tetrameric, but with the same arrangement of the rings within the crystal[22]. The structure of $(C_5H_5)_3Pr$ **4e** (Fig. 1) consists of a uniform polymer-chain with three η^5-coordinated cyclopentadienyl rings and one η^2-coordinated bridging ring for every Pr atom, thus resulting in a formal coordination number 11 for praseodymium[23].

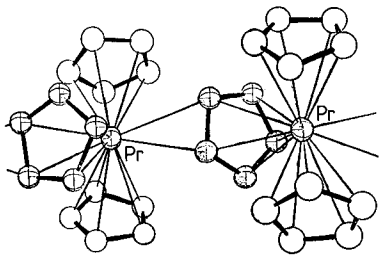


Fig. 1. Structure of $(C_5H_5)_3Pr$ **4e** in the crystal [23].

The unsaturated character of the compounds **4**, which is reflected in their structures, is also manifested in their behavior towards coordinating solvents such as THF[24-31], ammonia[6,26], pyridine[32], isocyanides[25,33,34], and phosphanes[25,35]. With these solvents they form remarkably stable 1:1 complexes in which the solvent molecule is bonded to the metal via oxygen, nitrogen, carbon, or phosphorus. As before, the three C_5H_5 rings are η^5-bonded. The compounds **4** also behave as Lewis acids towards phosphorus ylides[36] and carbonyl- or nitrosyl-complexes of the transition metals[37].

Only two substituted cyclopentadienyl ligands have so far been used successfully for the synthesis of triorganyllanthanoid compounds. Tris(methylcyclopentadienyl)metal compounds **6** of practically all lanthanoids can be obtained[28,37-40]. Furthermore, La, Pr and Nd form compounds of the type $(i\text{-}C_3H_7C_5H_4)_3Ln$ **7**[41]. With more bulky ligands, such as the pentamethylcyclopentadienyl, the trimethylsilylcyclopentadienyl, or even the bis(trimethylsilyl)cyclopentadienyl moiety, only the disubstituted derivatives could be obtained.

2.2. Cyclopentadienyllanthanoid Halides $(C_5H_5)_2LnCl$ and $C_5H_5LnCl_2\cdot(THF)_3$

A key role in the synthesis of organolanthanoid compounds with η^1-bonded organyls is played by the cyclopentadienyllanthanoid halides. The first species of type **8** were obtained by reaction of the lanthanoid trichlorides **3** with **1** in the molar ratio 1:2 or by comproportionation between **3** and **4**[42].

$$\underset{\mathbf{3}}{LnCl_3} + 2\,\underset{\mathbf{1}}{C_5H_5Na} \xrightarrow{THF} \underset{\mathbf{8}}{(C_5H_5)_2LnCl} + 2\,NaCl$$

Ln = Y (**8b**), Sm (**8h**), Gd (**8k**), Tb (**8l**), Dy (**8m**), Ho (**8n**), Er (**8o**), Tm (**8p**), Yb (**8q**), Lu (**8r**)

$$\underset{\mathbf{3}}{LnCl_3} + 2\,\underset{\mathbf{4}}{(C_5H_5)_3Ln} \xrightarrow{THF} 3\,\underset{\mathbf{8}}{(C_5H_5)_2LnCl}$$

Ln = Sm (**8h**), Gd (**8k**), Dy (**8m**), Ho (**8n**), Er (**8o**), Yb (**8q**)

$(C_5H_5)_2ScCl$ **8a** has been prepared from **3a** and $(C_5H_5)_2Mg$[43], while **8h** and **8q** were respectively obtained from **4h** and **4q** and NH_4Cl in benzene[44]. The cleavage of one Ln–C bond of the tricyclopentadienyllanthanoids **4**

by HCl has also been used for the synthesis of several of the species **8**[42]. With the exception of **8c**, **8d**, **8e**, **8f**, and **8g** all other compounds of this type could be isolated. In THF they form 1:1 complexes, $(C_5H_5)_2LnCl\cdot(THF)$ (**9**)[45-47], whereas in benzene solution or in the solid state the compounds form dimers in which the metal atoms are bridged by two chlorines, as could be deduced from the results of the X-ray structure analysis of **8a** (Fig. 2)[48]. Because of the larger ionic radii of the lighter lanthanoids La to Pm, a coordinative saturation of the metal will obviously not be reached with such a structure, thus making the isolation of these compounds from solutions impossible.

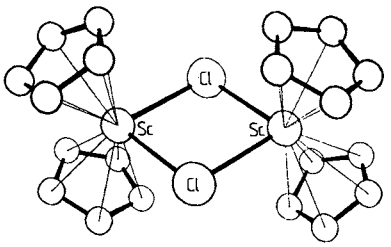
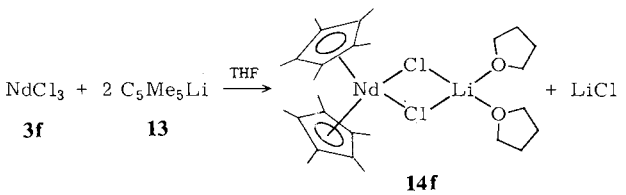


Fig. 2. Molecular structure of $[(C_5H_5)_2ScCl]_2$ **8a** in the crystal [48].

This situation changes if substituted cyclopentadienyl ligands are used. Although the only compounds of the type $(CH_3C_5H_4)_2LnCl$ **10** known so far are those from **10m**[37,42,49] onwards (there have been no reports concerning the corresponding derivatives of the remaining metals **a** to **l**), the observation that bis(pentamethylcyclopentadienyl)neodymium chloride **11f**[50] is an extremely stable compound which does not melt below 220°C, and the fact that the series of compounds of the type $[(Me_3Si)_2C_5H_3]_2LnCl$ **12**[51] is almost complete, unequivocally demonstrate the high screening effect of these bulky, substituted cyclopentadienyl ligands. Hence, compounds of the type Cp_2LnCl should also be stable in the case of the lighter metals.

The tendency of these metals to favor higher coordinative saturation leads to the compounds forming complexes with alkali metal halides[50,52-54] in which the lanthanoid and the alkali metal are bridged twice, in each case by an halogen atom, and in which the alkali metal is electronically further saturated by additional donor molecules such as THF or ether. An example is **14f**.



At this point two reactions should be mentioned. Firstly, the oxidation of $(C_5Me_5)_2Yb\cdot(dme)$ **15q** with $[(C_5H_5)_2Fe][PF_6]$, which leads to purple crystals of the composition $(C_5Me_5)_2YbPF_6\cdot(dme)$ **16q**[53], and, secondly, the reaction of ether-free $(C_5Me_5)_2Yb(\mu\text{-}Cl)_2Li$ **17q** with Al_2Cl_6, leading to the blue complex $(C_5Me_5)_2Yb(\mu\text{-}Cl)_2\text{-}AlCl_2$ **18q**, which loses aluminum chloride in THF and is converted into the complex $(C_5Me_5)_2YbCl\cdot(THF)$ **19q**[53] (dme = dimethoxyethane).

The use of the bis(trimethylsilyl)cyclopentadienyl ligand, introduced into synthesis by *Lappert* et al.[51,55], also enables the preparation and isolation of diorganometal chlorides **12**, even of the lighter lanthanides. Almost all lanthanoid trichlorides **3** react with bis(trimethylsilyl)cyclopentadienyl lithium **20** in THF to give complexes of the type $[(Me_3Si)_2C_5H_3]_2Ln(\mu\text{-}Cl)_2Li(THF)_2$ **21**, which decompose above 140°C with formation of the solvent-free derivatives **22**.

The X-ray structure analysis of **12e** as well as those of the isostructural scandium and ytterbium compounds, **12a** and **12q**, respectively, confirm the dimeric nature of the molecules with distorted tetrahedral ligand coordination around each lanthanoid atom. These dimers react with compounds RCl (R = large cation) to give very stable ionic complexes **23**—**26**[56,57].

$$RCl + 1/2\{[(Me_3Si)_2C_5H_3]_2LnCl\}_2 \rightarrow R^{\oplus}\{[(Me_3Si)_2C_5H_3]_2LnCl_2\}^{\ominus}$$
12 **23—26**

$R = N(PPh_3)_2$, Ln = Y (**23b**)
$R = PPh_4$, Ln = Pr (**24e**), Tm (**24p**)
$R = AsPh_4$, Ln = Nd (**25f**)
$R = PPh_3(CH_2Ph)$, Ln = Nd (**26f**), Dy (**26m**)

Finally, some analogous complexes with trimethylsilylcyclopentadienyl ligands have also been described, for example: $(Me_3SiC_5H_4)_2Y(\mu\text{-}Cl)_2Li\cdot L_x$ [L = THF, x = 2 (**27b**); L = tmed, x = 1 (**28b**)][58], the red-brown dimers $[(Me_3SiC_5H_4)_2YbX]_2$ [X = Cl (**29q**), I (**30q**)][59], and the complexes $(Me_3SiC_5H_4)_2Yb(\mu\text{-}Cl)_2Li(Et_2O)_2$ **31q** and $(Me_3SiC_5H_4)_2Lu(\mu\text{-}Cl)_2Li$ **32r**[54] (tmed = tetramethylenediamine).

The cyclopentadienyllanthanoid dichlorides **5**, which are prepared by reaction of **3** with **1** or by comproportionation of **3** and **4**[60], are monomeric. If they are prepared in THF, three solvent molecules remain in the coordination sphere of the metal. Figure 3 shows the arrangement of the ligands in compound **5o**[61]. La, Sm, Eu, Tm, and Yb also form complexes of the type $C_5H_5LnCl_2\cdot(THF)_4$ **33**[62]. The structure of the pentamethylcyclopentadienyllanthanoid dihalide-alkali halide complexes such as $C_5Me_5Nd(\mu\text{-}Cl)_3\text{-}Na\cdot(Et_2O)_2$ **34f**[50], $C_5Me_5Ln(\mu\text{-}Cl)_3Li\cdot(Et_2O)_2$ (Ln = Yb (**35q**[53], Lu (**35r**)[54]), $C_5Me_5Yb(\mu\text{-}Cl)_3Li\cdot(THF)$ **36q**[54], and $C_5Me_5Yb(\mu\text{-}I)_3Li\cdot(Et_2O)_2$ **37q**[53,54] is formulated with three halogen bridges.

Table 2 lists the most important data of the compounds **8** and **5**.

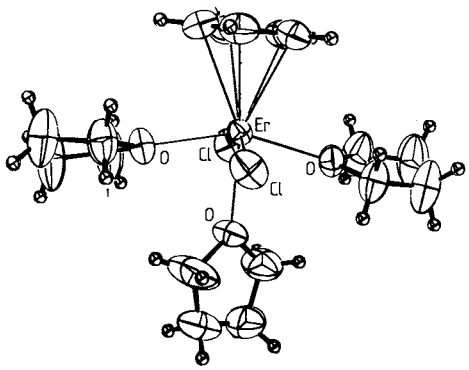


Fig. 3. Molecular structure of $C_5H_5ErCl_2\cdot(THF)_3$ **5o** in the crystal [61].

Table 2. Physical properties of dicyclopentadienyllanthanoid chlorides **8** and cyclopentadienyllanthanoid dichlorides **5**. dec = decomposition.

$(C_5H_5)_2LnCl$ **8** Ln		Color	M.p. [°C]	μ_{eff} [B. M.]	Ref.
Sc	**8a**	green-yellow	313–315	[d]	[2]
Y	**8b**	colorless	[a]	[d]	[63]
Sm	**8h**	yellow	200 (dec.)	1.62	[42]
Gd	**8k**	colorless	140 (dec.)	8.86	[42]
Tb	**8l**	colorless			[64]
Dy	**8m**	yellow	343–346	10.6	[42]
Ho	**8n**	yellow-orange	340–343	10.3	[42]
Er	**8o**	pink	200 (dec.)	9.79	[42]
Tm	**8p**	green-yellow	[b]		[63]
Yb	**8q**	orange-red	240 (dec.)	4.81	[42]
Lu	**8r**	colorless	318–320	[d]	[42]

$(C_5H_5)LnCl_2\cdot(THF)_3$ **5** Ln		Color	M.p. [°C]	μ_{eff} [B. M.]	Ref.
Y	**5b**				[65]
La	**5c**		65 (dec.)		[66]
Sm	**5h**	beige	50 (dec.)		[60]
Eu	**5i**	purple	50 (dec.)	4.24	[60]
Gd	**5k**	lavender	82–86 (dec.)		[60]
Dy	**5m**	colorless	85–90 (dec.)	11.81	[60]
Ho	**5n**	yellow	84–92		[60]
Er	**5o**	pink	91–94	9.68	[60]
Tm	**5p**		58–64 (dec.)		[66]
Yb	**5q**	orange	78–81	7.52	[60]
Lu	**5r**	colorless	[c]	[d]	[60]

[a] Sublimation at 250°C/10^{-3} torr. [b] Sublimation at 200°C/10^{-4} torr. [c] Sublimation at 150–250°C/10^{-5} torr. [d] Diamagnetic.

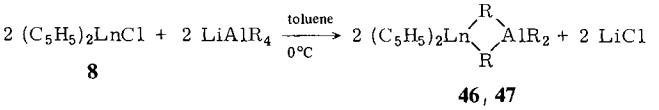
Elementary iodine reacts with **4o** with substitution and formation of the pink $(C_5H_5)_2ErI$ **38o**[42]. The compounds $(C_5H_5)_2NdCN$ **39f** and $(C_5H_5)_2YbCN$ **39q** have been prepared by reaction of **4f** and **4q**, respectively, with HCN[67].

Finally, it should be mentioned that $[(C_5H_5)_2YCH_3]_2$ **40b** reacts with CH_3AlCl_2 with cleavage of the Y–CH_3 bond and formation of the stable complex $(C_5H_5)_2Y(\mu\text{-}Cl)_2Al(CH_3)_2$ **41b**[63], and that the reaction of **8b** with AlH_3 in ether or in triethylamine yields the complexes $[(C_5H_5)_2YCl]_2\cdot AlH_3\cdot Et_2O$ **42b**[68] and $[(C_5H_5)_2YCl\cdot AlH_3\cdot NEt_3]_2$ **43b**[69], respectively.

2.3. Alkyl- and Aryl(dicyclopentadienyl)lanthanoid Complexes

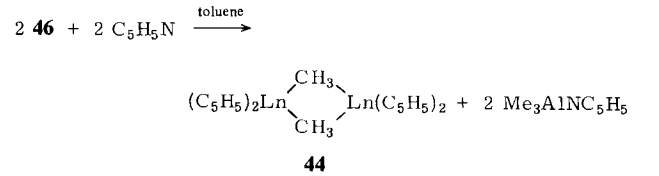
Alkyl- and aryl(dicyclopentadienyl)lanthanoid complexes are accessible by reaction of **8** with Grignard reagents or alkyl- and aryllithium compounds. Generally speaking, such compounds are dimers, **44**, and not monomers as initially postulated by *Tsutsui* and *Ely*[70,71]. Monomeric molecules must be stabilized, either intramolecularly by a chelating ligand, as is the case in $(C_5H_5)_2ScC_6H_4CH_2NMe_2$–(*o*) **45a**[72], or intermolecularly by coordinating solvents.

Accordingly, the species **8** react with lithium tetraalkylaluminates in toluene to give the complexes **46** or **47**, respectively[73,74]. These complexes are converted by pyridine into the dimeric dicyclopentadienyl(methyl)lanthanoid complexes **44**, which compensate their electron deficiency by forming methyl bridges between the two lanthanoid atoms (Fig. 4)[63,75]. In contrast, reaction of **46a** with pyridine does not furnish **44a**, but the monomeric dicyclopentadienyl(methyl)pyridinescandium **48a**[63,75].



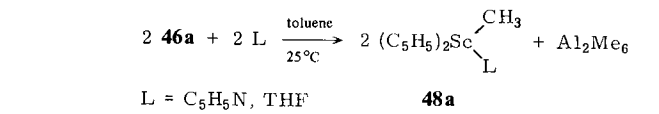
8 **46, 47**

R = CH_3, Ln = Sc (**46a**), Y (**46b**), Gd (**46k**), Dy (**46m**), Ho (**46n**), Er (**46o**), Tm (**46p**), Yb (**46q**)
R = C_2H_5, Ln = Sc (**47a**), Y (**47b**), Ho (**47n**)



44

Ln = Y (**44b**), Dy (**44m**), Ho (**44n**), Er (**44o**), Tm (**44p**), Yb (**44q**)



L = C_5H_5N, THF **48a**

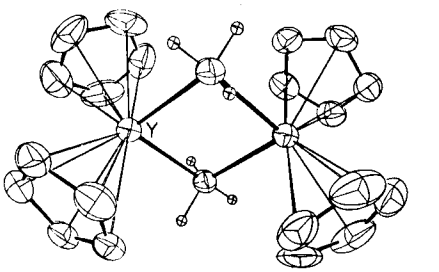
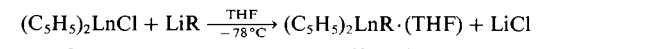


Fig. 4. Molecular structure of $[(C_5H_5)_2YCH_3]_2$ **44b** in the crystal [63].

8r reacts with alkyl- and aryllithium compounds in tetrahydrofuran to give monomeric 1 : 1 complexes of the alkyl- and aryl(dicyclopentadienyl)lutetium derivatives with THF, respectively. **49r**, **50r**, **51r**, and **52r** can only be detected by NMR at room temperature, whereas the corresponding compounds with more or less bulky alkyl or aryl ligands can be isolated as colorless to light-yellow, needle-like crystals[76–78]. Analogous THF-complexes have also been obtained with yttrium[49], samarium[77,79], gadolinium[80], erbium[49,77,80], thulium[77,79], and ytterbium[77,79,80]:



8 **49–58**

R = CH_3,	Ln = Lu (**49r**)
R = C_2H_5,	Ln = Lu (**50r**)
R = *i*-C_3H_7,	Ln = Lu (**51r**)
R = *n*-C_4H_9,	Ln = Sm (**52h**), Tm (**52p**), Yb (**52q**), Lu (**52r**)
R = *t*-C_4H_9,	Ln = Y (**53b**), Sm (**53h**), Er (**53o**), Tm (**53p**), Yb (**53q**), Lu (**53r**)
R = $CH_2C(CH_3)_3$,	Ln = Lu (**54r**)
R = CH_2SiMe_3,	Ln = Er (**55o**), Yb (**55q**), Lu (**55r**)
R = $CH_2C_6H_5$,	Ln = Lu (**56r**)
R = $C_6H_4CH_3$-(*p*),	Ln = Gd (**57k**), Er (**57o**), Yb (**57q**), Lu (**57r**)
R = C_6H_4Cl-(*p*),	Ln = Er (**58o**)

In compounds **49r** to **57r** the lutetium atom is located at the centroid of a distorted tetrahedron formed by the centers of two cyclopentadienyl ligands, the η^1-bonded carbon atom, and the oxygen atom of the THF (Fig. 5)[77].

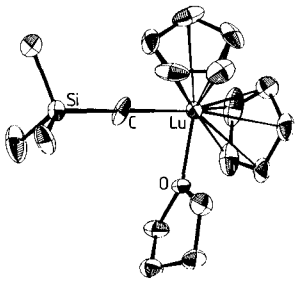
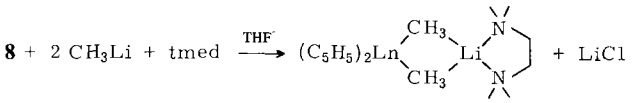


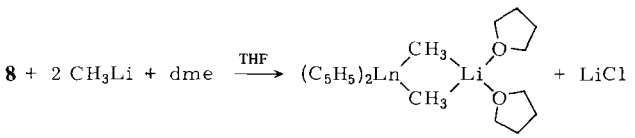
Fig. 5. Molecular structure of $(C_5H_5)_2LuCH_2SiMe_3 \cdot (THF)$ **55r** in the crystal [77].

8o and **8r** react with an excess of methyllithium in THF in the presence of tmed to give complexes **59**, in which the two methyl groups bridge the lanthanoid and the lithium, and which are further stabilized by coordination of a tmed molecule to the lithium.

If dme is used instead of tmed, the complexes **60** containing two molecules of the solvent THF are formed[81].



Ln = Er (**59o**), Lu (**59r**) **59**



Ln = Er (**60o**), Lu (**60r**) **60**

The X-ray structure analysis of **59o** shows a tetrahedrally coordinated erbium atom and a lithium atom which is also coordinated tetrahedrally by two methyl groups and the two nitrogens of the tmed ligand (Fig. 6)[81].

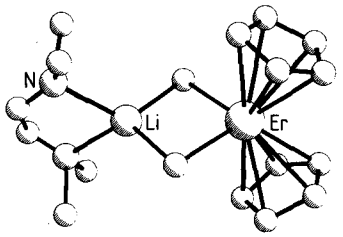


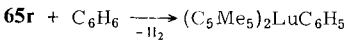
Fig. 6. Molecular structure of $(C_5H_5)_2Er(\mu\text{-}CH_3)_2Li \cdot (tmed)$ **59o** in the crystal [81].

The pentamethylcyclopentadienyl derivatives $(C_5Me_5)_2Yb(\mu\text{-}Cl)(\mu\text{-}CH_3)Li \cdot (Et_2O)_2$ **61q** and $(C_5Me_5)_2Yb(\mu\text{-}CH_3)_2Li \cdot (Et_2O)_2$ **62q** have been obtained by reaction of $(C_5Me_5)_2Yb(\mu\text{-}Cl)_2Li \cdot (Et_2O)_2$ **63q** with CH_3Li in THF[53].

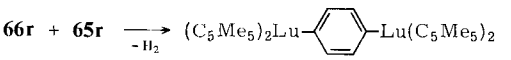
The corresponding lutetium derivatives, especially **64r**, the first monomer not stabilized by solvent molecules, can be used as novel Ziegler-catalysts. They promote the formation of longer alkyl chains from olefins[82,83] and activate C–H bonds[84,85]. Thus, **64r** reacts with H_2 to form **65r**, which in turn reacts with benzene with elimination of H_2 to yield the compounds **66r** and **67r**[84]. The reactions of

$(C_5Me_5)_2LuCH_3$ **64r**

$(C_5Me_5)_2LuH$ **65r**

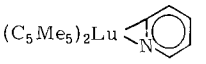


66r



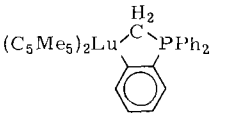
67r

64r with pyridine, tetramethylsilane, and methylene(triphenyl)phosphorane proceed with elimination of methane[84]:



68r

$(C_5Me_5)_2LuCH_2SiMe_3$ **69r**



70r

2.4. Allyl- and Alkynyl(cyclopentadienyl)lanthanoid Compounds

The allyl(dicyclopentadienyl) derivatives of scandium[43], samarium, holmium, and erbium[86], which are readily accessible from **8** and allylmagnesium chloride, have a fluctional allyl group. However, the exact structure of these compounds is still unknown. According to NMR investigations, $(C_5Me_5)_2LuCH_2C(CH_3)=CH_2$ **72r**, which is formed as a decomposition product of $(C_5Me_5)_2Lu\text{–}i\text{-}C_4H_9$ **71r**, also has a fluctional structure[83].

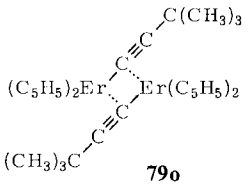
The first alkynyl derivatives of the lanthanoids, the scandium[43], gadolinium, holmium, erbium, and ytterbium derivatives $(C_5H_5)_2LnC{\equiv}CC_6H_5$ **73**[71,87] as well as $C_5H_5Ho(C{\equiv}CC_6H_5)_2$ **74n**[71], have been prepared from $(C_5H_5)_2LnCl$ **8** and $C_5H_5HoCl_2 \cdot (THF)_3$ **5n** and alkali metal phenylacetylide, respectively. Reaction of **4f** or **4q** with acetylene derivatives likewise affords species of this kind (**75**–**78**)[88]:

$$(C_5H_5)_3Ln + HC{\equiv}CR \longrightarrow (C_5H_5)_2LnC{\equiv}CR + C_5H_6$$

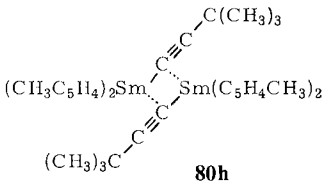
4 **73, 75–78**

Ln	R = C_6H_5	*n*-C_4H_9	*n*-C_6H_{13}	*c*-C_6H_{11}	$C_5H_5FeC_5H_4$
Nd	**73f**	**75f**	**76f**	**77f**	**78f**
Yb	**73q**	**75q**	**76q**	**77q**	**78q**

X-ray structure analyses of **79o**[89,90] and **80h**[91] show the molecules to be dimeric with bridging α-C atoms.



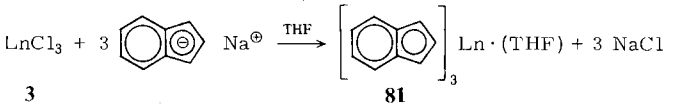
79o



80h

2.5. Compounds with Indenyl, Cyclooctatetraenyl, and other π-Ligands

Triindenyllanthanoids were first prepared in 1968 by *Tsutsui* by the reaction of **3** with indenylsodium and were isolated as THF-adducts **81**[7,92]:



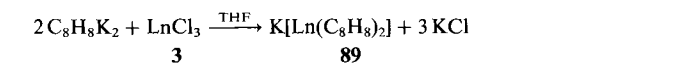
Ln = La (**81c**), Sm (**81h**), Gd (**81k**), Tb (**81l**), Dy (**81m**), Yb (**81q**)

Solvent-free $(C_9H_7)_3Sm$ **82h** is formed on reaction of **3h** with $(C_9H_7)_2Mg$ in benzene. The X-ray structure analysis of this compound shows that the samarium atom is surrounded, in a trigonal planar manner, by the centers of the five-membered rings of the three indenyl moieties[93]. The structure of $(C_9H_7)_3Ce \cdot (C_5H_5N)$ **83d**, which is prepared by the reduction of $Ce(O\text{-}i\text{-}C_3H_7)_4 \cdot (C_5H_5N)$ with triethylaluminum in indene, confirms the π-complexation for the indenyl derivatives. The π-bonded five-membered moieties of the three indenyl ligands and the σ-bonded nitrogen atom of the pyridine are arranged tetrahedrally around the cerium atom[94].

Depending on the stoichiometry, reaction of **3** with heptamethylindenylsodium in THF affords $(C_9Me_7)_3Ln$ **84**, $(C_9Me_7)_2LnCl$ **85**, or $C_9Me_7LnCl_2$ **86**, which are coordinated with different amounts of THF[95].

Fluorenyl derivatives of the lanthanoids have been described by two research groups: the bright yellow trifluorenyl cerium **87d** was reported first[96], and then the complexes $(C_{13}H_9)_2Ln(\mu\text{-}Cl)_2Li \cdot (THF)_2$ **88** with Ln = La (**88c**), Sm (**88h**), and Ho (**88n**)[97].

Compounds of the lanthanoids in the oxidation state +3 with cyclooctatetraene were first reported in 1970[98]. The reactions of **3** with $C_8H_8K_2$ in tetrahydrofuran afford the complexes **89**, which are stable up to ca. 160 °C but sensitive towards air and moisture[98–100].



Ln = Sc (**89a**), Y (**89b**), La (**89c**), Ce (**89d**), Pr (**89e**), Nd (**89f**), Sm (**89h**), Gd (**89k**), Tb (**89l**)

Infrared, Raman, visible and ultraviolet spectra[101], semiempirical LCAO calculations[102], and the chemical behavior are consistent with strong ionic bonding between lanthanoid and cyclooctatetraene.

Cerium complexes with the potassium cation additionally coordinated by one monoglyme[103] or diglyme molecule[104] have also been described. The X-ray structure analysis of the diglyme complex **90d** shows a discrete $[Ce(C_8H_8)_2]^{\ominus}$ anion with planar C_8H_8 rings. The potassium cation is coordinated by the diglyme on one side and by one of the cyclooctatetraenyl rings on the other side (Fig. 7).

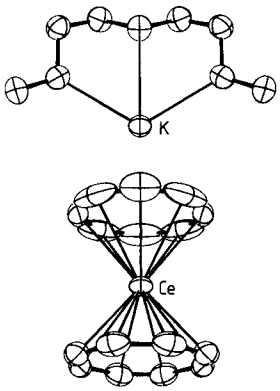
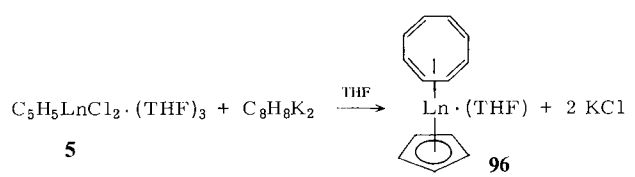


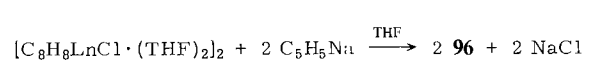
Fig. 7. Molecular structure of $[K(diglyme)][Ce(C_8H_8)_2]$ **90d** in the crystal [104].

The reactions of **3** in THF with only one equivalent of $K_2C_8H_8$ afford complexes of the type $[C_8H_8LnCl \cdot (THF)_2]_2$ **91**[99,105,106]. Investigation of the structure of the cerium complex **91d** provided proof of its dimeric nature, and showed that the two cerium atoms are bridged asymmetrically by two chlorine atoms and are each coordinated to one cyclooctatetraenyl ring and two THF molecules[107]. The complexes lose the tetrahydrofuran on heating above 60 °C in vacuo. Reaction of **91r** with Me_3SiCH_2Li or *o*-$Me_2NCH_2C_6H_4Li$ in THF afforded the first cyclooctatetraenyl(organyl)lutetium compounds $(C_8H_8)LuR \cdot (THF)$ with $R = CH_2SiMe_3$ **92r** or $C_6H_4CH_2NMe_2$-(*o*) **93r**, respectively[108].

Cocondensation of La, Ce, Nd, or Er metal atoms with cyclooctatetraene at 77 K and subsequent extraction of the reaction product with THF furnished the binuclear complexes $[C_8H_8Ln(THF)_2][Ln(C_8H_8)_2]$ **94**[109]. The neodymium compound **94f** crystallizes with an asymmetrically bridging cyclooctatetraenyl ring between the two neodymium atoms[109,110]. A triple-decker sandwich structure is assumed for the green microcrystalline $(C_8H_8)_3Ce_2$ **95d**[103] formed on reaction of $Ce(O\text{-}i\text{-}C_3H_7)_4$ with triethylaluminum in presence of cyclooctatetraene.



Ln = Y (**96b**), Sm (**96h**), Ho (**96n**), Er (**96o**)



Ln = Y (**96b**), Nd (**96f**)

Sandwich complexes **96** with two different 'flaps' can be obtained either by reaction of **5** with $C_8H_8K_2$, or of **91** with **1**, in THF[65].

The analogous scandium compound **96a** is formed in a solvent-free state from $C_8H_8ScCl\cdot(THF)$ and **1** as a yellowish, air-sensitive powder[100,106].

Dicyclopentadienyllanthanoid chlorides in which the cyclopentadienyl rings are bridged one with the other are formed when **3** is allowed to react with the disodium salt of 1,3-dicyclopentadienylpropane in THF[111,112]. With this new ligand it was possible for the first time to synthesize dicyclopentadienyllanthanoid chlorides of the earlier lanthanoids praseodymium and neodymium as THF-complexes **97**. The THF ligand can be exchanged for other bases, such as for instance 2,2'-bipyridine[113].

$$\underset{\mathbf{3}}{LnCl_3} + NaC_5H_4(CH_2)_3C_5H_4Na \xrightarrow{THF} \underset{\mathbf{97}}{LnCl\cdot(THF)} + 2\,NaCl$$

Ln = La (**97c**), Ce (**97d**), Pr (**97e**), Nd (**97f**), Gd (**97k**), Dy (**97m**), Ho (**97n**), Er (**97o**), Yb (**97q**), Lu (**97r**)

Finally, it should be pointed out that **3f** and 2,4-dimethylpentadienylpotassium react in tetrahydrofuran to yield the, so-to-speak 'open' pentadienyl complex **98f** as a brilliant green, ionic compound. The molecule contains a ring-shaped array of three almost planar pentadienyl ligands, each of which has two methyl groups in the 2- and 4-positions protruding out from the plane and bent away from the neodymium atom[114].

$$\underset{\mathbf{3f}}{NdCl_3} + 3\,C_7H_{11}K \xrightarrow{THF} \underset{\mathbf{98f}}{Nd} + 3\,KCl$$

2.6. Homoleptic Organolanthanoid Compounds

The simplest organometallic compounds of the lanthanoids in the oxidation state +3 are the species $(CH_3)_3Ln$. Since the inner transition elements strive to reach high coordination numbers it can be expected that these compounds exhibit a high reactivity. Hence, for a long time, only indirect evidence could be found for the existence of simple homoleptic organolanthanoid compounds; the isolation and characterization of compounds belonging to this class were first achieved in the last decade[115].

2.6.1. Neutral Homoleptic Organolanthanoid Compounds

3a and **3b** react with methyl- or phenyllithium with formation of air-sensitive products, of which only the phenyl derivatives **99** could be characterized by analysis, IR spectroscopy, and reactions with $HgCl_2$, CO_2 or benzophenone[9,10]:

$$\underset{\mathbf{3}}{LnCl_3} + 3\,C_6H_5Li \xrightarrow{THF} \underset{\mathbf{99}}{(C_6H_5)_3Ln} + 3\,LiCl$$

Ln = Sc (**99a**), Y (**99b**)

Bulky ligands such as *tert*-butyl, neopentyl, or trimethylsilylmethyl can improve the stability of homoleptic organolanthanoid compounds considerably. However, whereas the trimethylsilylmethyl derivatives **100** and **101** still require THF as additional stabilizing ligand, the complexes **102b** and **103a** are stable as monomers without any coordinated solvent molecules[116,117]. The complexes **100**, prepared by reaction of $ErCl_3$ or $TmCl_3$ with Me_3SiCH_2Li in THF at −78 °C, lose one THF ligand when warmed to 0 °C and yield the fivefold coordinated complexes **101**[118,119] With the corresponding ytterbium or lutetium derivative this transition from sixfold to fivefold coordination takes place even at −25 °C[58,119].

$$\underset{\mathbf{3}}{LnCl_3} + 3\,Me_3SiCH_2Li \xrightarrow{THF} \underset{\mathbf{100}}{(Me_3SiCH_2)_3Ln\cdot(THF)_3} + 3\,LiCl$$

Ln = Er (**100o**), Tm (**100p**)

$$\mathbf{100} \xrightarrow{-25\,^\circ C} \underset{\mathbf{101}}{(Me_3SiCH_2)_3Ln\cdot(THF)_2} + THF$$

Ln = Er (**101o**), Tm (**101p**), Yb (**101q**), Lu (**101r**)

$[(Me_3Si)_2CH]_3Y$ **102b**
$[(o\text{-}CH_3OC_6H_4SiMe_2)_2CH]_3Sc$ **103a**

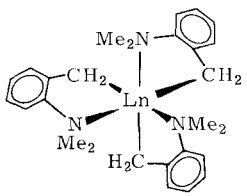
The ^1H- and ^{13}C-NMR data of **101r** are consistent with a trigonal bipyramidal structure with the THF ligands occupying the axial positions. On prolonged standing at 40 °C in an inert atmosphere, **101o** and **101r** split off not only the two residual THF ligands but also tetramethylsilane to give the pyrophoric, polymeric carbene complexes **104**[119].

$$\mathbf{101} \xrightarrow[-2\,THF]{40\,^\circ C} 1/n[Ln(CH_2SiMe_3)(CHSiMe_3)]_n + Si(CH_3)_4$$
$$\mathbf{104}$$

Ln = Er (**104o**), Lu (**104r**)

The products of the reactions of YCl_3 or $NdCl_3$ with $C_6H_5CH_2Li$, $C_6H_5C(CH_3)_2CH_2Li$, or Me_3SiCH_2Li decompose in a similar manner. The compounds expected to be formed, namely $(C_6H_5CH_2)_3Ln$ **105**, $[C_6H_5C(CH_3)_2CH_2]_3Ln$ **106**, and $(Me_3SiCH_2)_3Ln$, respectively, could not be isolated[120–122].

By using ligands containing built-in chelating groups, such as terminal amino groups, it is possible to synthesize solvent-free homoleptic organolanthanoid compounds. Thus, *o*-$Me_2NC_6H_4CH_2Li$ and *o*-$Me_2NCH_2C_6H_4Li$ react with **3a**, **3b**, **3c**, **3f**, and **3o** to give the sixfold coordinated compounds **107** and **108**, respectively[72,123].



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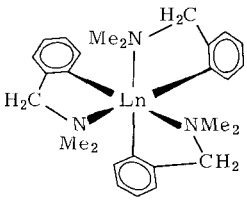
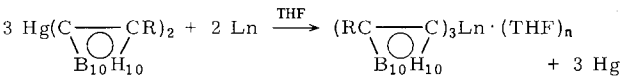


108

The carbaboranyl derivatives **109** and **110** of La, Tm and Yb were obtained by reaction of the *C*-mercurio deriv-

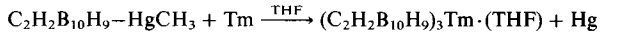
atives of methyl- and phenylcarbaborane with the metals in THF at 20°C[124]. A carbaboranyl derivative with a thulium-boron bond, **111p**, has also been described[125].



109, **110**

R = CH_3, Ln = Tm, n = 3 (**109p**); Yb, n = 2 (**109q**)

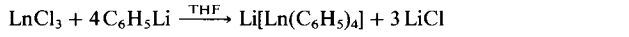
R = C_6H_5, Ln = La, n = 1 (**110c**); Tm, n = 3 (**110p**); Yb, n = 2 (**110q**)



111p

2.6.2. *Anionic Homoleptic Organolanthanoid Compounds*

$LaCl_3$ and $PrCl_3$ react with phenyllithium to give the homoleptic organometallic compounds **112** in which four phenyl groups are bound to the metal[10].



3 **112**

Ln = La (**112c**), Pr (**112e**)

A tetrahedral ligand arrangement is suggested for the anion $[Ln(C_6H_5)_4]^{\ominus}$; such an arrangement has already been established in the case of the anion of the analogously prepared $[Li(THF)_4][Lu(C_6H_3Me_2)_4]$ **113r** (Fig. 8)[126].

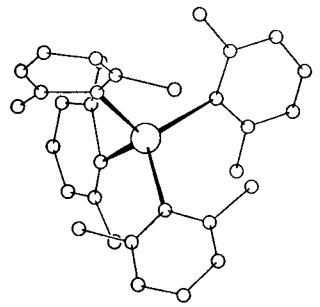
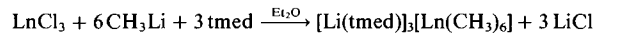
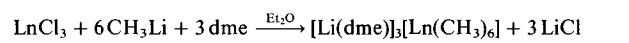


Fig. 8. Structure of the anion of $[Li(THF)_4][Lu(C_6H_3Me_2)_4]$ **113r** in the crystal [126].

In 1978, the first permethylated complexes of the lanthanoids could be synthesized with the aid of tmed as stabilizing base[127]. In the meantime, the hexamethyl complexes **114** of nearly all the lanthanoids have been synthesized by reaction of stoichiometric amounts of **3**, $LiCH_3$, and tmed[128–130]. The radioactive element promethium was the only lanthanoid not included in these investigations, while $EuCl_3$ is reduced by $LiCH_3$ to europium(II) compounds of unknown structure[130]. Analogous, but thermally less stable complexes **115** can be prepared by using dme instead of tmed[130, 131].



3 **114**



3 **115**

Table 3. Physical properties of hexamethyllanthanoid derivatives **114** and **115**.

$[Li(tmed)]_3[Ln(CH_3)_6]$ **114** Ln		Color	Dec. [°C]	Ref.
Sc	**114a**	colorless	94–98	[130]
Y	**114b**	colorless	120–132	[129]
La	**114c**	colorless	79–82	[129]
Ce	**114d**	yellow	86–89	[130]
Pr	**114e**	green	59–62	[129]
Nd	**114f**	violet	78–83	[129]
Sm	**114h**	yellow	85–88	[129]
Gd	**114k**	greenish	112	[129]
Tb	**114l**	colorless	115	[129]
Dy	**114m**	colorless	106	[129]
Ho	**114n**	yellowish	122	[129]
Er	**114o**	pink	122–125	[129]
Tm	**114p**	greenish	109–114	[129]
Yb	**114q**	yellow	116–126	[129]
Lu	**114r**	colorless	142	[129]

$[Li(dme)]_3[Ln(CH_3)_6]$ **115** Ln		Color	Dec. [°C]	Ref.
Y	**115b**	colorless	49–52	[130]
Ce	**115d**	yellow	51–53	[130]
Nd	**115f**	blue	46–48	[130]
Sm	**115h**	yellow	48–50	[130]
Gd	**115k**	yellowish	83–85	[130]
Tb	**115l**	colorless	72–74	[130]
Dy	**115m**	colorless	68–69	[130]
Er	**115o**	pink	82–84	[131]
Lu	**115r**	colorless	84–88	[131]

Table 3 lists the colors and decomposition points of these compounds. The X-ray structure analyses of **114o**[128], **114n** (Fig. 9)[129], and **115r**[131] show that the lanthanoid atoms are surrounded by six methyl groups in a slightly distorted octahedral arrangement. All Ln–C bonds are of equal length, and the six methyl groups bridge the lanthanoid atom pairwise with the three lithium atoms. The lithium atoms are each located at the center of a tetrahedron formed by the two bridging methyl groups and the two nitrogen or oxygen atoms of the tmed or dme ligand.

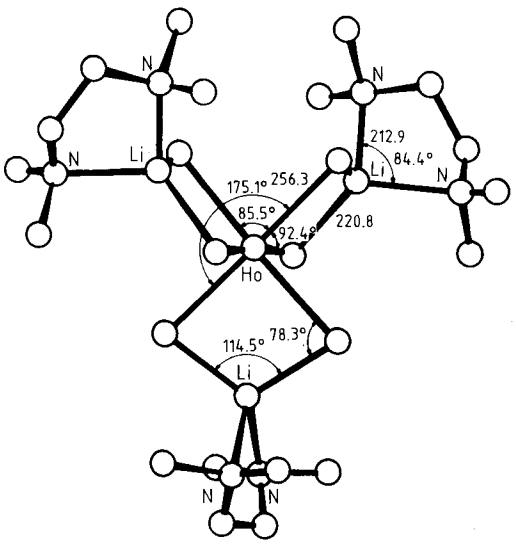
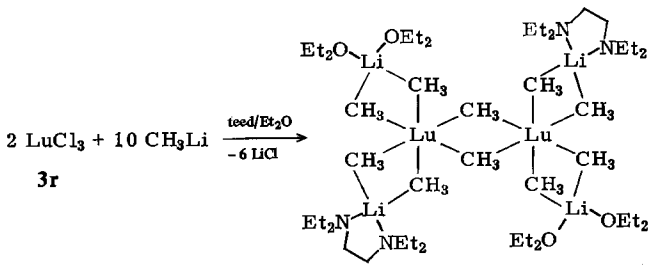


Fig. 9. Molecular structure of $[Li(tmed)]_3[Ho(CH_3)_6]$ **114n** in the crystal [129].

Even polynuclear methyl derivatives of the lanthanoids are capable of existence, as is demonstrated by compound **116r**, which could be isolated on reaction of **3r** with

CH_3Li. In this compound there are methyl bridges not only between lutetium atoms and lithium atoms but also between two lutetium atoms (teed = tetraethylethylenediamine)[131].



116r

Lanthanoid trichlorides **3** or *tert*-butoxides react with *t*-C_4H_9Li to give tetrahedrally structured complex anions, with the lithium ion coordinated by three or four THF, four Et_2O, or two tmed molecules, depending on the solvent used in the reactions[129,132,133].

$$LnCl_3 + 4\,t\text{-}C_4H_9Li \xrightarrow{THF} [Li(THF)_x][Ln(t\text{-}C_4H_9)_4] + 3\,LiCl$$
3 → **117, 118**

Ln = Yb, x = 3 (**117q**); Ln = Er, x = 4 (**118o**)

$$LnCl_3 + 4\,t\text{-}C_4H_9Li \xrightarrow[Et_2O]{pentane} [Li(Et_2O)_4][Ln(t\text{-}C_4H_9)_4] + 3\,LiCl$$
3 → **119**

Ln = Tb (**119l**), Er (**119o**), Lu (**119r**)

$$Ln(O\text{-}t\text{-}C_4H_9)_3 + 4\,t\text{-}C_4H_9Li \xrightarrow[tmed]{pentane} [Li(tmed)_2][Ln(t\text{-}C_4H_9)_4] + 3\,t\text{-}C_4H_9OLi$$
120

Ln = Er (**120o**), Lu (**120r**)

Complexes of the type $[LiL_4][Ln(CH_2SiMe_3)_4]$ with L = THF **121** or Et_2O **122** or L_2 = tmed **123** are formed in the reaction of Me_3SiCH_2Li with either the neutral, homoleptic compound **101** or with **3**[58,119].

$$(Me_3SiCH_2)_3Ln\cdot(THF)_2 + Me_3SiCH_2Li \xrightarrow{THF} [LiL_4][Ln(CH_2SiMe_3)_4]$$
101 → **121, 123**

L = THF, Ln = Y (**121b**)
L_2 = tmed, Ln = Y (**123b**), Er (**123o**), Yb (**123q**)

$$LuCl_3 + 4\,Me_3SiCH_2Li \xrightarrow{Et_2O} [Li(Et_2O)_4][Lu(CH_2SiMe_3)_4] + 3\,LiCl$$
3r → **122r**

$$\mathbf{122r} + 2\,tmed \longrightarrow [Li(tmed)_2][Lu(CH_2SiMe_3)_4] + 4\,Et_2O$$
123r

The complexes **122** and **123** also decompose slowly at room temperature with loss of tetramethylsilane and formation of products in which not only CH_2SiMe_3 but also $CHSiMe_3$ and $CSiMe_3$ groups are fixed to the lanthanoids[134].

$ErCl_3$ and $YbCl_3$ react with $(Me_3Si)_2CHLi$ in THF to give complexes of the type $[Li(THF)_4]\{Ln[CH(SiMe_3)_2]_3Cl\}$ **124**. On heating in hexane solution, the erbium compound **124o** is converted into a lithium salt containing the $\{Er[CH(SiMe_3)_2]_4\}^{\ominus}$ anion[58].

2.7. Organolanthanoid Hydrides

Organolanthanoid hydrides were first prepared in 1981/82 by hydrogenolysis of alkyl(dicyclopentadienyl)lanthanoid derivatives[47,49]. The X-ray structure analyses of **126b**[49], **126o**[49], and **65f**[135] confirm a hydrogen-bridged dimeric structure. In the case of **65h** the bulky pentamethylcyclopentadienyl ligands prevent coordination of additional solvent molecules.

$$[(C_5Me_5)_2SmC(H_5C_6)=C(C_6H_5)Sm(C_5Me_5)_2] + H_2 \longrightarrow [(C_5Me_5)_2SmH]_2$$
65h

$$2\,Cp_2LnR\cdot(THF) + 2\,H_2 \xrightarrow{toluene} [Cp_2LnH\cdot(THF)]_2 + 2\,RH$$
125, 126

Cp = C_5H_5, R = *t*-C_4H_9, Ln = Y (**125b**); R = *t*-C_4H_9, Ln = Er (**125o**); R = *t*-C_4H_9, $CH_2C(CH_3)_3$, CH_2SiMe_3, $CH_2C_6H_5$, Ln = Lu (**125r**)
Cp = $CH_3C_5H_4$, R = *t*-C_4H_9, Ln = Y (**126b**), Er (**126o**), Lu (**126r**)

The hydrides **65**, **125**, and **126** undergo very interesting reactions. Thus, **126b** reacts with *t*-C_4H_9NC to yield $[(CH_3C_5H_4)_2Y(HC{=}N\text{-}t\text{-}C_4H_9)]_2$ **127b**[136], and **65r**, which according to its NMR spectrum rapidly equilibrates with the monomeric species at 25 °C, catalyzes the polymerization of olefins and activates C–H bonds, even in $Si(CH_3)_4$[82–84].

$$2\,(C_5Me_5)_2LuCH_3 + 2\,H_2 \xrightarrow[20°C]{hexane} [(C_5Me_5)_2LuH]_2 + 2\,CH_4$$
64r → **65r**

$$(C_5Me_5)_2Lu(\mu\text{-}H)_2Lu(C_5Me_5)_2 \rightleftharpoons 2\,(C_5Me_5)_2LuH$$
65r

$$(C_5Me_5)_2LuH \xrightarrow[-H_2]{+Si(CH_3)_4} (C_5Me_5)_2LuCH_2SiMe_3$$
69r

The tetrahydridoborates **128** and **129** are readily accessible by reaction of the corresponding chlorides with $NaBH_4$ in tetrahydrofuran[56,77,137].

$$Cp_2LnCl\cdot(THF) + NaBH_4 \xrightarrow{THF} Cp_2LnBH_4\cdot(THF) + NaCl$$
128, 129

Cp = C_5H_5, Ln = Sm (**128h**), Er (**128o**), Yb (**128q**), Lu (**128r**)
Cp = $(Me_3Si)_2C_5H_3$, Ln = Sc (**129a**), Y (**129b**), La (**129c**), Pr (**129e**), Nd (**129f**), Sm (**129h**), Yb (**129q**)

The IR spectra of **129c**, **129e**, **129f**, and **129h** suggest a tridentate BH_4 ligand, whereas the spectra of **129b** and **129q** are better interpreted in terms of a bidentate BH_4 ligand[56]. The structure determinations carried out on solvent-free **129a** unequivocally prove the presence of a rigid bidentate BH_4 ligand[56].

Novel types of polynuclear organolanthanoid hydrides are formed when Cp_2LnR derivatives decompose by β-elimination. The compounds $[Li(THF)_3][\{(C_5H_5)_2LuH\}_3H]$

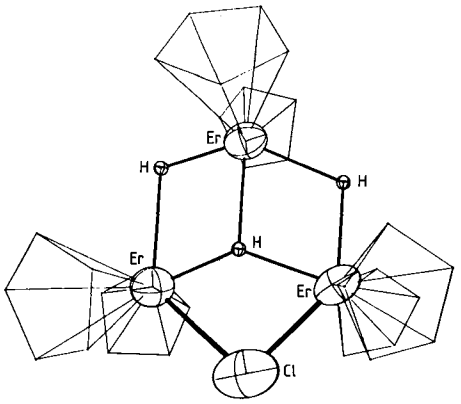


Fig. 10. Structure of the anion of $[Li(THF)_4][\{(C_5H_5)_2ErH\}_3Cl]$ **131o** in the crystal [138].

130r and $[Li(THF)_4][\{(C_5H_5)_2ErH\}_3Cl]$ **131o** (Fig. 10) have been obtained in this way[138]. **8r** reacts with NaH in THF in a way not yet clear, to yield $[Na(THF)_6][\{(C_5H_5)_3Lu\}_2H\cdot(THF)_2]$ **132r** (Fig. 11)[139]. Finally, it should be mentioned that the condensation of Sm, Er, or Yb vapor with 1-hexyne at 77 K affords catalytically active polymers which contain $[(n\text{-}C_4H_9C{\equiv}C)_2SmH]$, $[(n\text{-}C_4H_9C{\equiv}C)_2ErH]$, or $[(n\text{-}C_4H_9C{\equiv}C)_3Yb_2H]$ moieties, respectively[140].

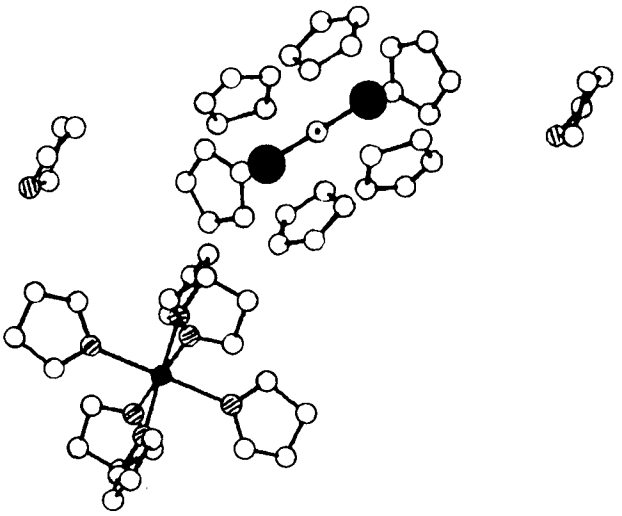


Fig. 11. Structure of $[Na(THF)_6][(C_5H_5)_3LuHLu(C_5H_5)_3]\cdot(THF)_2$ **132r** in the crystal [139]; ● Lu, ○ C, ◍ O, ⊙ H, • Na.

$$LnCl_3 + 3\ (CH_3)_3P{=}CH_2 \longrightarrow Ln[CH_2P(CH_3)_3Cl]_3$$

3

$-3\ LiCl,\ -3\ C_4H_{10}$ ↓ $+3\ LiC_4H_9$

Ln = La (**133c**), Pr (**133e**), Nd (**133f**), Sm (**133h**), Gd (**133k**), Ho (**133n**), Er (**133o**), Lu (**133r**)

$$Ln\left[\begin{matrix}CH_2\\ \\ CH_2\end{matrix}\!\!>\!P(CH_3)_2\right]_3$$

133

2.8. Ylide Complexes of the Lanthanoids

The first ylide complexes **133** of the lanthanoids were synthesized in 1976 using trimethyl(methylene)phosphorane as starting material; they are very sensitive to air and moisture[141].

The complex ^{1}H-NMR spectra suggest a temperature-dependent equilibrium between the monomeric species **133** and the oligomeric and polymeric species. This could be demonstrated by means of ^{1}H-, ^{13}C-, and ^{31}P-NMR spectra (Fig. 12) in the case of the analogous complex

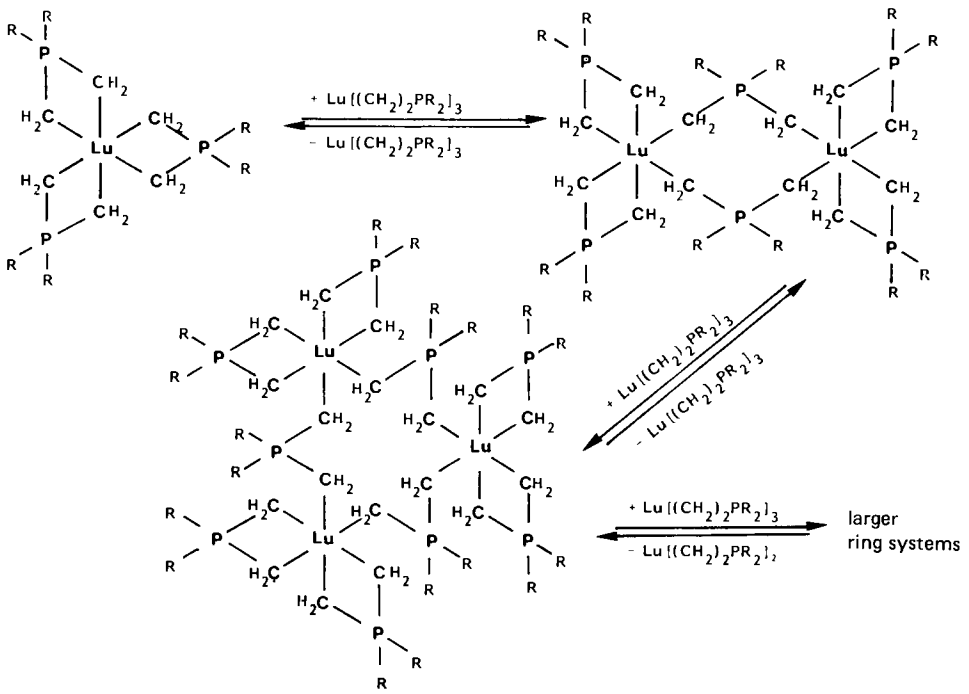
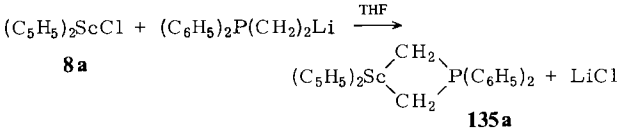
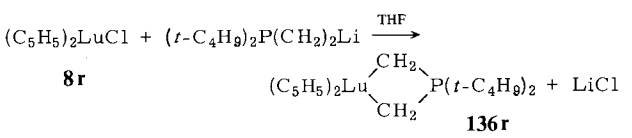


Fig. 12. Oligomerization equilibrium in $Lu[(CH_2)_2P(t\text{-}C_4H_9)_2]_3$ **134r** [142]; $R = t\text{-}C_4H_9$.

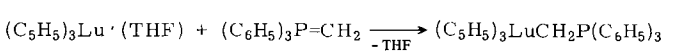
134r, which is accessible from $LuCl_3$ **3r** and $(t\text{-}C_4H_9)_2P(CH_2)Li$[142].

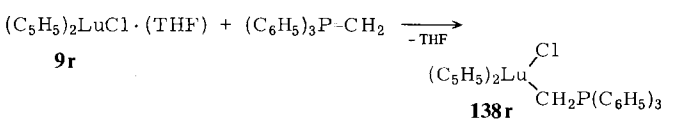
Dicyclopentadienyllanthanoid ylide complexes, such as **135a**[143] and **136r**[142], which are prepared in THF, are, however, monomeric in benzene.

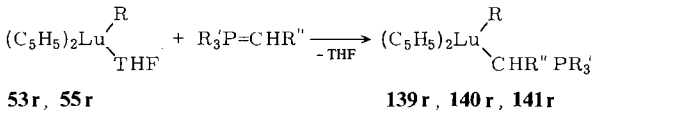




Phosphorus ylides can replace THF as stabilizing base in organolanthanoid compounds, as is shown by the following exchange reactions of **4r**·(THF), **9r**, **53r**, and **55r**, which already proceed at low temperatures in THF or toluene solution[36, 144, 145].

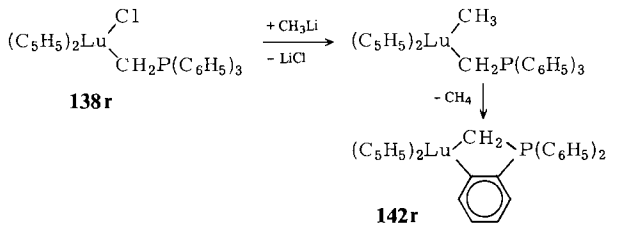






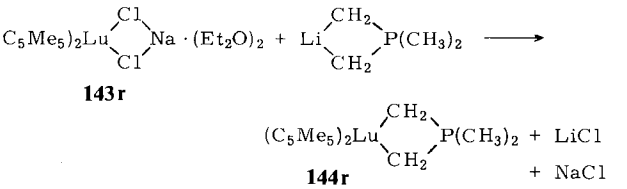
R = t-C_4H_9, R' = C_6H_5, R'' = H (**139r**)
R = CH_2SiMe_3, R' = C_6H_5, R'' = H (**140r**)
R = t-C_4H_9, R' = CH_3, R'' = $SiMe_3$ (**141r**)

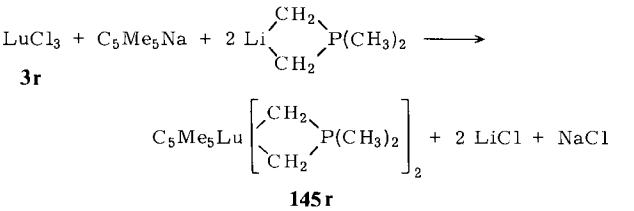
Of special interest is the zwitterionic complex **138r**, which is stable up to 172°C, hydrolyzes with cleavage of all Lu–C bonds, and is converted by an intramolecular metalation of one phenyl ring into **142r** on reaction with $LiCH_3$ at −78°C[36, 146].



The cyclic ylide **142r** is also accessible from **138r** and NaH, or by the reaction of **9r** with t-C_4H_9Li in the presence of $(C_6H_5)_3P{=}CH_2$[36, 146]. Reaction of **64** or **65** with $(C_6H_5)_3P{=}CH_2$ also yields a cyclic ylide complex (**70**)[84].

Pentamethylcyclopentadienyllutetium complexes with $(CH_2)_2P(CH_3)_2$ as chelating ligand are remarkably thermally stable[147].





The composition and structure of the complex **144r**, which melts with decomposition at 205°C, could be confirmed by X-ray structure analysis (Fig. 13)[147].

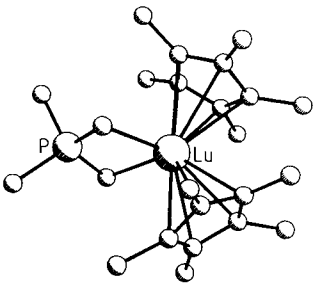
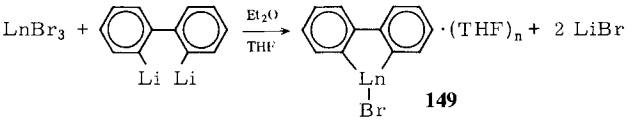


Fig. 13. Molecular structure of $(C_5Me_5)_2Lu(CH_2)_2P(CH_3)_2$ **144r** in the crystal [147].

2.9. Organolanthanoid-Element Compounds

2.9.1. Compounds with Lanthanoid-Main Group Element Bonds

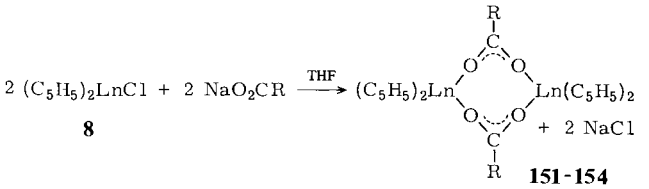
Shortly after the first synthesis of the tricyclopentadienyl derivatives **4**, the cyclopentadienyllanthanoid halides **5** and **8** were prepared as the first organolanthanoid compounds with additional bonds between the lanthanoid and another element other than carbon. They are the most important starting materials for the synthesis of other organolanthanoid derivatives with bonds between the lanthanoids and other elements of the periodic table. Besides the cyclopentadienyl-, indenyl-, fluorenyl- and cyclooctatetraenyllanthanoid halides and the compound $(CH_3)_2C{=}C(C_6H_5)$-$ScCl_2\cdot(THF)_3$ **146a**, first mentioned in 1979[148], the following organolanthanoid halides have been described: the triphenylmethyllanthanoid dichlorides of La (**147c**)[149], Pr (**147e**), Nd (**147f**), Gd (**147k**), and Ho (**147h**)[150], the fluorenyl derivatives $(C_{13}H_9)_2Ln(\mu\text{-}Cl)_2Li\cdot(THF)_2$ of La (**148c**), Nd (**148f**), Sm (**148h**), Ho (**148n**), and Lu (**148r**)[151], and the methyl- and phenylcarbaboranyllanthanoid chlorides of La, Tm, and Yb[125]. Even metallacycles **149** have also been reported[152].



Ln = Pr (**149e**), Gd (**149k**), Ho (**149n**), Yb (**149q**)

Dicyclopentadienyllanthanoid alkoxides were prepared from **8** and the corresponding sodium alkoxides[42,77], or, as shown for $(C_5Me_5)_2LuOC_2H_5$ **150r**, by ethanolysis of **64r**[84].

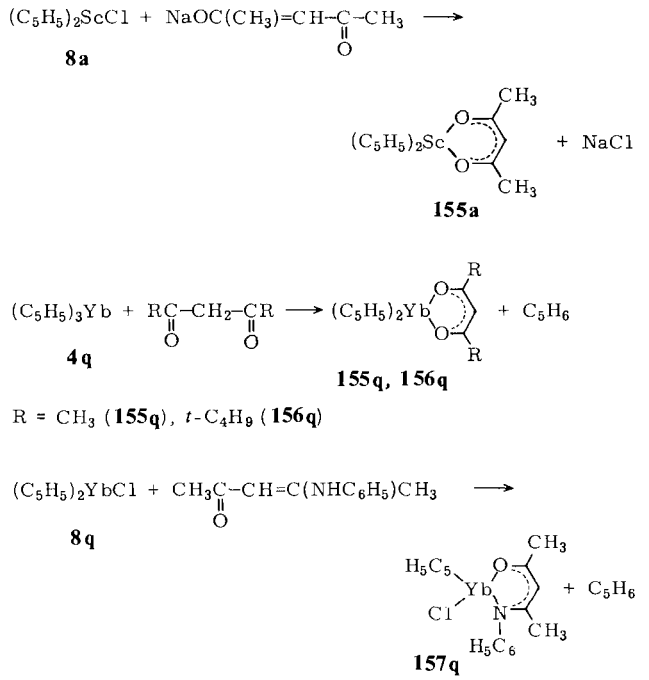
The dicyclopentadienyllanthanoid carboxylates **151**—**154**, which can be prepared from **8** and alkali metal carboxylates, are dimeric in boiling benzene[42,43,88].



8 **151-154**

R = H; Ln = Er (**151o**), Yb (**151q**)
R = CH_3; Ln = Sc (**152a**), Er (**152o**), Yb (**152q**)
R = *n*-C_4H_9; Ln = Yb (**153q**)
R = C_6H_5; Ln = Yb (**154q**)

Reaction of **8a** with sodium acetylacetonate[43] or of **4q** with β-diketones[153] affords the dionates **155a**[43], **155q** and **156q**, respectively[153]. β-Aminoketones react with **8q** analogously to give **157q**[153].



8a **155a**

4q **155q, 156q**

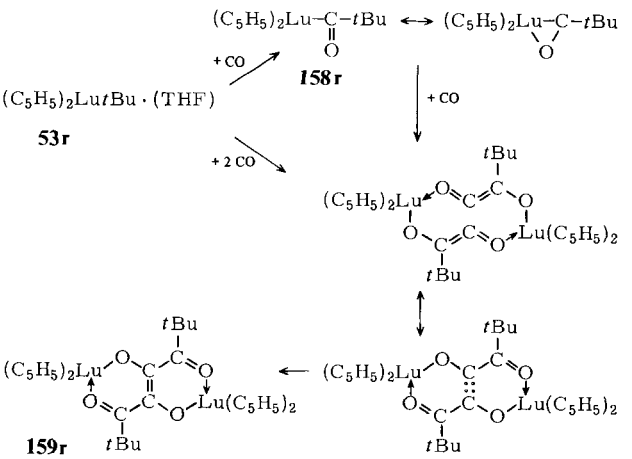
R = CH_3 (**155q**), *t*-C_4H_9 (**156q**)

8q **157q**

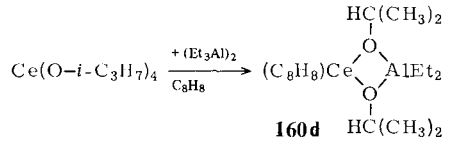
53r reacts with CO to give a yellow acyl complex **158r**, which, after insertion of a second CO molecule, dimerizes to the complex **159r**, the structure of which has been confirmed X-ray crystallographically. It has been suggested that ketene-carbene intermediates are formed during the course of this reaction[154].

Reduction of $Ce(O-i-C_3H_7)_4$ with triethylaluminum in the presence of cyclooctatetraene yields the yellow cerium(III) complex **160d** with two alkoxy bridges between Ce and Al[155].

The first organolanthanoid sulfur compounds have recently been obtained by reaction of bis(pentamethylcyclopentadienyl)neodymium or -ytterbium chloride with sodium dithiocarbamate. In the ytterbium derivative **161q** the dithiocarbamate group functions as a bidentate ligand (Fig. 14)[156].



53r **158r** **159r**



160d

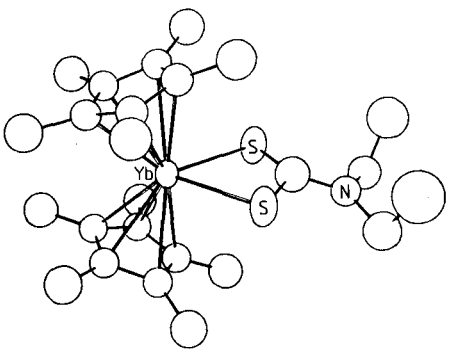
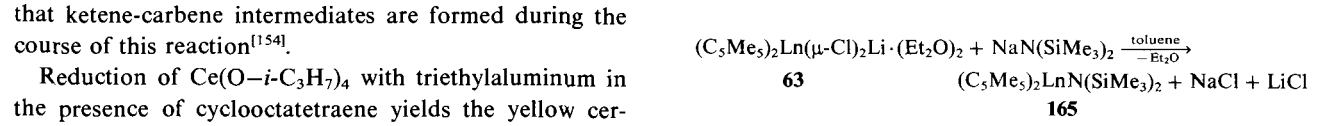


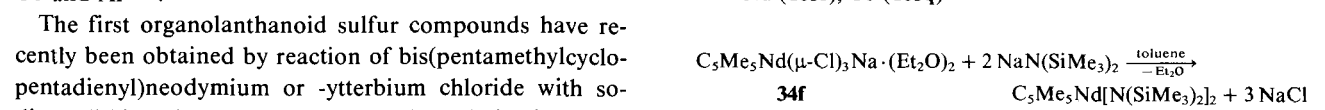
Fig. 14. Molecular structure of $(C_5Me_5)_2YbS_2CNEt_2$ **161q** in the crystal [156].

The first organolanthanoid-nitrogen compound was prepared as long ago as 1963 by reaction of **8o** with $NaNH_2$[42]. A couple of years later, it could be shown that $(C_5H_5)_2YbNH_2$ **163q** is the product of the thermal decomposition of $(C_5H_5)_3Yb\cdot(NH_3)$ **162q** at 250 °C[25]. Furthermore, besides the well known homoleptic compounds $Ln[N(SiMe_3)_2]_3$ **164**[157], the bis(trimethylsilyl)amido derivatives **165** and **166** have also been described[50].



63 **165**

Ln = Nd (**165f**), Yb (**165q**)



34f **166f**

Like its analogue **127b**, the formimidoyl complex **167b** (Fig. 15), which is formed on reaction of **125b** with *t*-C_4H_9NC, also contains a Y–N bond[136].

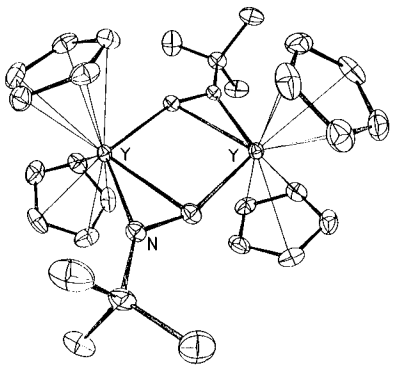


Fig. 15. Molecular structure of $[(C_5H_5)_2Y(HC{=}N{-}t\text{-}C_4H_9)]_2$ **167b** in the crystal [136].

The first dicyclopentadienyllanthanoid phosphides **168** and **169** have been prepared, starting from $LiP(t\text{-}C_4H_9)_2$[64,158] and $LiP(t\text{-}C_4H_9)(C_6H_5)$[158], respectively.

$$(C_5H_5)_2LnCl + LiP(t\text{-}C_4H_9)R \xrightarrow{THF} (C_5H_5)_2Ln{-}P(t\text{-}C_4H_9)R + LiCl$$

8 **168**, **169**

	R	Ln = Tb	Ho	Er	Tm	Yb	Lu
168	t-C_4H_9	**l**	**u**	**o**	**p**	**q**	**r**
169	C_6H_5	**l**	**u**	**o**		**q**	**r**

Some diphenyl-[35,91] and dicyclohexylphosphane derivatives[35] as well as homoleptic compounds of the type $Ln[P(t\text{-}C_4H_9)_2]_3$ **170**[159] and their arsene analogues $Ln[As(t\text{-}C_4H_9)_2]_3$ **171**[160] have also been described. However, no exact determinations of the structure of these compounds have been carried out as yet.

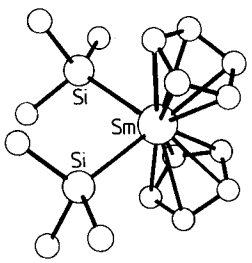


Fig. 16. Structure of the anion in $[Li(dme)_2][(C_5H_5)_2Sm(SiMe_3)_2]$ **172h** in the crystal [161].

The X-ray structure analysis of the first compound containing a Ln–Si bond (**172h**) (Fig. 16) shows that an ionic complex containing two Sm–Si bonds is formed on reaction of **8h** with $LiSiMe_3$ in dme, even when a molar ratio of 1:1 is used[161]. The corresponding compounds of germanium (**173**) and tin (**174**) can also be prepared[162]. These compounds, as well as the complexes of the type **175**, are extremely sensitive to oxygen[163–165].

$$(C_5H_5)_2LnCl\cdot(THF) + LiM(C_6H_5)_3 \xrightarrow{THF}$$
9

$$(C_5H_5)_2Ln{-}M(C_6H_5)_3 + LiCl$$
173, **174**

Ln = Er, M = Ge (**173o**)
Ln = Er, M = Sn (**174o**); Ln = Yb, M = Sn (**174q**)

$[(Me_3Si)_2N]_mLn[Sn(CH_2SiMe_3)_3]_{3-m}\cdot(dme)$; m = 0, 2, 3
Ln = Pr (**175e**), Nd (**175f**)

2.9.2. Compounds with Lanthanoid-Transition Metal Bonds

Very few organolanthanoid compounds containing lanthanoid-transition metal bonds have so far been described in the literature. The first experiments aimed at the preparation of such compounds, carried out as long ago as 1973, showed that $(C_5H_5)_3Ln$ **4** reacts with carbonyl- or nitrosyl metal compounds, but, the composition and the structure of the reaction products are still unknown[37,166]. The infrared spectra of the complexes formed on reaction of **4h** with salts of the manganese-containing anions $[Mn(CO)_5L]^{\ominus}$ have been interpreted in terms of Sm–Mn bonds[167]. On the other hand, well-defined complexes **176** and **177**, which are stable up to 220 °C, can be prepared from **8** and **10**[37].

$$Cp_2LnCl + Na[W(C_5H_5)(CO)_3] \xrightarrow{THF}$$
8, **10**

$$Cp_2Ln{-}W(C_5H_5)(CO)_3 + NaCl$$
176, **177**

Cp = C_5H_5, Ln = Dy (**176m**), Er (**176o**), Yb (**176q**)
Cp = $CH_3C_5H_4$, Ln = Dy (**177m**), Ho (**177n**)

The two complexes with Yb–Co (**179q** (Fig. 17)) and Yb–Fe bonds (**180q** (Fig. 18)) were obtained by reaction of $(C_5Me_5)_2Yb\cdot(Et_2O)$ **178q** with $Co_2(CO)_8$[168] and **178q** with $Fe_2(CO)_9$ or $Fe_3(CO)_{12}$[169], respectively.

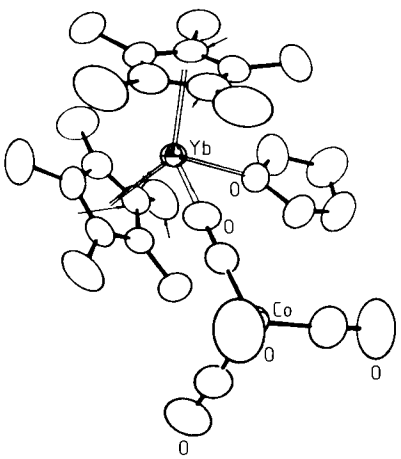


Fig. 17. Molecular structure of $(C_5Me_5)_2YbCo(CO)_4\cdot(THF)$ **179q** in the crystal [168].

Pure lanthanoid-transition metal compounds without any organic ligand on the lanthanoid atom, e.g. $Er[Co(CO)_4]_3\cdot(THF)_4$ **181o**[170], $[(CO)_4Co]HoCl_2\cdot(THF)_4$ **182n**[171], $\{[(C_6F_5)_3Ge]_7Cd_2\}Pr\cdot(dme)_3$ **183e**[172], and $[(C_6F_5)_3Ge]_7Hg_2Ho\cdot(dme)_3$ **184n**[173] have been synthesized

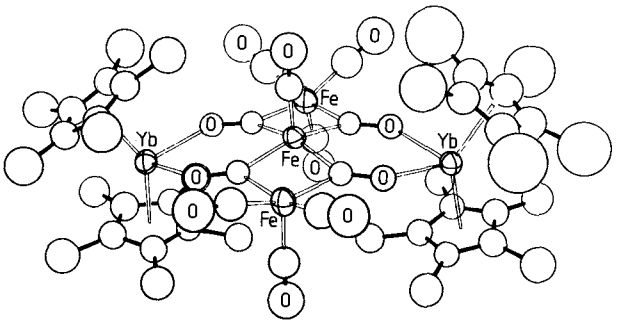


Fig. 18. Molecular structure of $[(C_5Me_5)_2Yb]_2[Fe_3(CO)_{11}]$ **180q** in the crystal [169].

by reaction of $LnCl_3$ **3** with carbonylmetal derivatives, or by reaction of lanthanoid amides or alkoxides with organomercury compounds.

3. Organometallic Compounds with Lanthanoids in the Oxidation State +2

When, in 1964, the blue solution of metallic europium in liquid ammonia was allowed to react with cyclopentadiene, and the crude product of the reaction was sublimed at 400 °C in vacuo, the ammonia-free sandwich complex **185i** was obtained as the first organometallic compound of a lanthanoid in the oxidation state +2[174]. The ytterbium complex **185q** has been prepared in an analogous way[14].

$$Ln + 3\,C_5H_6 \xrightarrow{\text{liq. } NH_3} \underset{\textbf{185}}{(C_5H_5)_2Ln} + C_5H_8$$

Ln = Eu (**185i**), Yb (**185q**)

In the meantime, other routes have been used successfully for the synthesis of **185q** as well as **186h**, **186i**, and **186q**[26,66,175].

$$\underset{\textbf{8q}}{(C_5H_5)_2YbCl} + Na \xrightarrow{THF} \underset{\textbf{185q}}{(C_5H_5)_2Yb} + NaCl$$

$$3\,\textbf{8q} + Yb \xrightarrow{THF} 3\,\textbf{185q} + YbCl_3$$

$$\underset{\textbf{4q}}{(C_5H_5)_3Yb} + Na \xrightarrow{THF} \underset{\textbf{185q}}{(C_5H_5)_2Yb} + C_5H_5Na$$

$$m\,Ln + (C_5H_5)_2Hg \xrightarrow{THF} (m-1)Ln/Hg + \underset{\textbf{186}}{(C_5H_5)_2Ln\cdot(THF)_n}$$

Ln = Sm (**186h**), Eu (**186i**), Yb (**186q**)

185i was one of the first compounds to be investigated by ^{151}Eu Mössbauer spectroscopy[176,177]. The green complex **185q** dissolves in THF to give a red solution, from which the yellow THF-complex **186q** can be isolated[26]. A red form of $(C_5H_5)_2Yb$ is also described in the literature[178,179].

$(C_5H_5)_3Sm$ **4h** is reduced by naphthalene potassium in the presence of THF to the purple, pyrophoric **186h**[180]. Ytterbium reacts with TlC_5H_5 in dme and in the presence of a little mercury to give the complex $(C_5H_5)_2Yb\cdot(dme)$ **187q**[31], in which the Yb atom is tetrahedrally surrounded by the centers of the two cyclopentadienyl rings and the two oxygen atoms of the dme molecule[181]. The yellow complex $(CH_3C_5H_4)_2Yb\cdot(THF)$ **188q**, which has been synthesized via several different routes, shows a helical chain structure consisting of $(CH_3C_5H_4)Yb(THF)$ units which are bridged by a further methylcyclopentadienyl ligand (Fig. 19)[182].

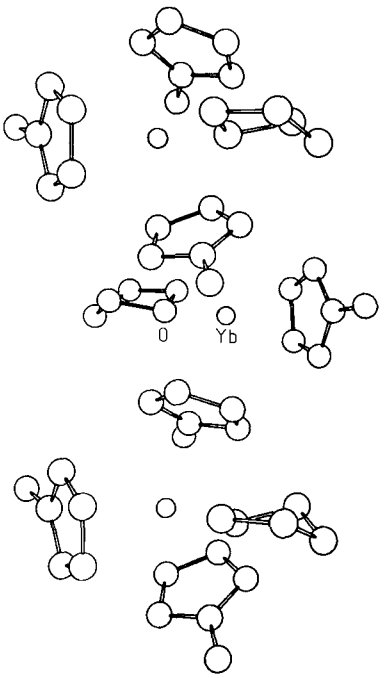


Fig. 19. Chain arrangement of the ligands in $(CH_3C_5H_4)_2Yb\cdot(THF)$ **188q** in the crystal [182].

Reduction of $[(Me_3SiC_5H_4)_2YbCl]_2$ **29q** with sodium amalgam in tetrahydrofuran yields the purple diamagnetic complex $(Me_3SiC_5H_4)_2Yb\cdot(THF)_2$ **189q**, which, on heating in vacuo, loses both THF ligands to give the green, solvent-free complex **190q**. Reaction of **189q** with tmed leads to formation of blue $(Me_3SiC_5H_4)_2Yb\cdot(tmed)$ **191q**[59].

Complexes $(C_5Me_5)_2Ln\cdot(L)$ (L = THF (**192**) or Et_2O (**178**)) of Sm^{II}, Eu^{II}, and Yb^{II} are formed on reaction of $LnCl_2$ or $LnCl_3$ with C_5Me_5Na in THF or Et_2O[183].

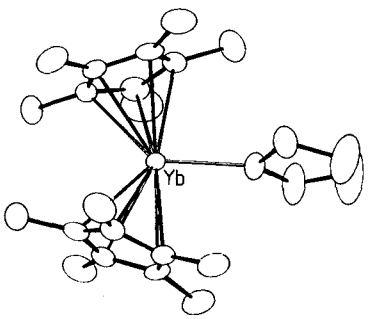


Fig. 20. Molecular structure of $(C_5Me_5)_2Yb\cdot(THF)\cdot(CH_3C_6H_5)_{1/2}$ **193q** in the crystal. The toluene not coordinated to Yb is not shown [183].

When **192q** is recrystallized from toluene, the hemitoluene complex $(C_5Me_5)_2Yb\cdot(THF)\cdot(C_6H_5Me)_{1/2}$ **193q** (Fig. 20) precipitates, the molecules of which form an

open sandwich structure with the ytterbium atom coordinated to the two C_5Me_5 rings and to the oxygen atom of the THF molecule, but not to the toluene[183]. Compounds of the type $(C_5Me_5)_2Yb \cdot L_2$ (L = THF (**194q**), Et_2O (**195q**); L_2 = dme (**15q**)) were synthesized from $YbBr_2$ and C_5Me_5Na. On heating, the red complex **194q** is converted via loss of a THF ligand into the orange complex **192q**[53]. The samarium derivative **194h** could be obtained by metal-atom synthesis from Sm and C_5Me_5H in hexane at

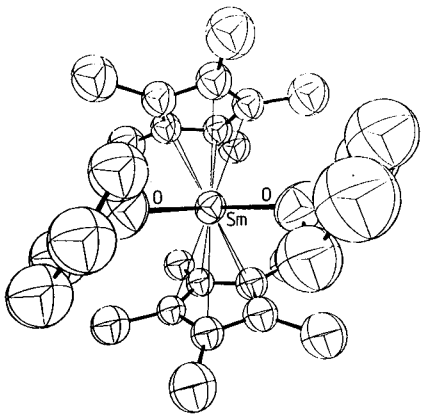
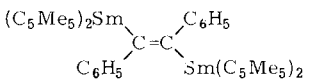


Fig. 21. Molecular structure of $(C_5Me_5)_2Sm \cdot (THF)_2$ **194h** in the crystal [184].

−120°C. The purple crystals show a sandwich structure with the THF-coordinated samarium atom located between the two pentamethylcyclopentadienyl rings (Fig. 21)[184]. **194h** reacts with diphenylacetylene to yield the black enediyl compound **196h**, which upon hydrolysis generates pure *trans*-stilbene[136].

$$(C_5Me_5)_2Sm \cdot (THF)_2 + C_6H_5C{\equiv}CC_6H_5 \xrightarrow{-THF}$$

194h



196h

Pyridine and *P,P'*-methylene- and *P,P'*-ethylenebis(dimethylphosphane) coordinate via N and P respectively to $(C_5Me_5)Ln$, as could be shown by the synthesis and elucidation of the structure of $(C_5Me_5)_2Yb \cdot (C_5H_5N)_2$ (**185q**)[185] and $(C_5Me_5)_2Ln \cdot L$ (Ln = Eu and Yb; L = $Me_2PCH_2PMe_2$ (**197**) or $Me_2PCH_2CH_2PMe_2$ (**198**))[186].

The orange compounds **199i** and **199q** are formed when europium and ytterbium, respectively, are allowed to react with cyclooctatetraene in liquid ammonia[8,109].

$$Ln + C_8H_8 \xrightarrow{\text{liq. } NH_3} (C_8H_8)Ln \quad \mathbf{199}$$

Ln = Eu (**199i**), Yb (**199q**)

Even cerium can be stabilized as Ce(II) by C_8H_8 ligands, as is shown by the reduction of $(C_8H_8)_2Ce$ **200d** with potassium in monoglyme. The green, microcrystalline **201d** is formed[103].

$$\underset{\mathbf{200d}}{(C_8H_8)_2Ce} + 2K \xrightarrow[30°C]{\text{monoglyme}} \underset{\mathbf{201d}}{[K(\text{monoglyme})]_2[Ce(C_8H_8)_2]}$$

Europium, samarium, and ytterbium react with alkyl or aryl iodides in THF between −20 and +30°C to yield the organolanthanoid(II) iodides **202**—**206**.

$$Ln + RI \xrightarrow{THF} R{-}Ln{-}I \quad \mathbf{202-206}$$

R = CH_3 (**202**); C_6H_5 (**203**), $C_6H_4CH_3$-(*p*) (**204**), $C_6H_3(CH_3)_2$-2,6 (**205**), $C_6H_2(CH_3)_3$-2,4,6 (**206**); Ln = Eu, Sm, Yb

The colored solutions, from which no well-defined compounds can be isolated, behave like Grignard compounds[187,188]. Thus, **203q** reacts with ketones and aldehydes to give alcohols, with esters to give alcohols and ketones, and with nitriles, albeit in low yields, to give ketones[189]. In contrast to the corresponding Grignard reaction, the reaction of **203q** with benzoyl chloride selectively affords benzophenone[190]. Both **203i** and **203q** react with $C_6H_5CF{=}CF_2$ in THF to yield *trans*-α,β-difluorostilbene[191].

Europium and ytterbium react with acetylene derivatives such as 1-propyne[192], 1-hexyne[193], or phenylacetylene[194] as well as with $Hg(C{\equiv}CC_6H_5)_2$[194], forming the isolable lanthanoid(II) compounds **207**—**209**. The compound **209q**, which is also obtainable from **210q** and $C_6H_5C{\equiv}CH$[194], reacts with aldehydes R'CHO and ketones R'_2CO to give (after hydrolysis) the alcohols $(C_6H_5C{\equiv}C)R'CHOH$ and $(C_6H_5C{\equiv}C)R'_2COH$, respectively. Benzophenone is reduced to benzopinacol[195].

$$Eu + 2CH_3C{\equiv}CH \xrightarrow{\text{liq. } NH_3} \underset{\mathbf{207i}}{(CH_3C{\equiv}C)_2Eu} + H_2$$

$$Ln + (RC{\equiv}C)_2Hg \xrightarrow{THF} \underset{\mathbf{208,\ 209}}{(RC{\equiv}C)_2Ln} + Hg$$

R = *n*-C_4H_9, Ln = Eu (**208i**); Yb (**208q**)
R = C_6H_5, Ln = Yb (**209q**)

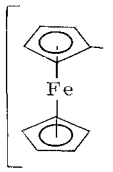
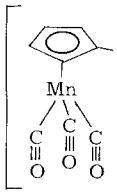
$$\underset{\mathbf{210q}}{(C_6F_5)_2Yb} + 2HC{\equiv}CC_6H_5 \xrightarrow{THF} \underset{\mathbf{209q}}{(C_6H_5C{\equiv}C)_2Yb} + 2C_6HF_5$$

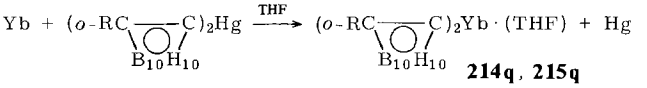
210q[196–198] and **210i**[198] are formed by transmetalation from $(C_6F_5)_2Hg$ and Yb or Eu, respectively. Of the less stable complexes $(C_6HF_4)_2Ln$ **211**, with the hydrogen in the 2- or 4-position of the phenyl ring, only the ytterbium derivative but not that of samarium could be isolated in a pure state[197,198].

$$Yb + (C_6F_5)_2Hg \xrightarrow{THF} \underset{\mathbf{210q}}{(C_6F_5)_2Yb} + Hg$$

210q is a useful reagent for incorporating the C_6F_5 group into transition metal complexes[198,199].

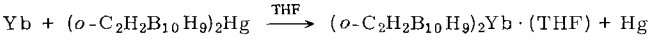
The metal exchange reaction between mercury and ytterbium has even enabled the preparation of ferrocene- **212q** and cymantrene- **213q**[200] as well as the carbaborane-derivatives **214q**—**216q**[124,152,201].

212q  **213q** 



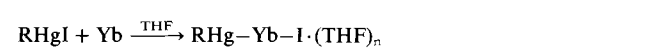
214q, **215q**

R = CH_3 (**214q**), C_6H_5 (**215q**)



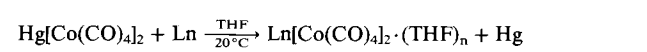
216q

Finally, it should be mentioned that organomercurioytterbium(II) iodides **217q**[202] and carbonyl derivatives of Sm, Eu, and Yb (**218**)[203] are also known.



217q

R = CF_3, C_5H_5, n = 2–4



218

Ln = Sm, Eu, Yb; n = 3, 4

4. Organometallic Compounds with Lanthanoids in the Oxidation State +4

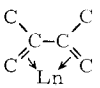
If there is any chance of being able to isolate organometallic compounds of the lanthanoids in the oxidation state +4, it should be possible in the case of cerium, where the electron configuration of the noble gas xenon is achieved on giving up four electrons. The first paper referring to the successful synthesis of $(C_5H_5)_4Ce$ and $(C_9H_7)_4Ce$[204] was published in 1971. In 1983, however, it could be proven that the reaction of C_5H_5Na with $[C_5H_6N]_2[CeCl_6]$ in THF yields exclusively $(C_5H_5)_3Ce$ **4d**, and not the long contested $(C_5H_5)_4Ce$[205]. Moreover, the reputed synthesis of $(C_9H_7)_4Ce$[206] is also in doubt, for it could never be repeated[103]. Therefore, compounds of the type $(C_5H_5)_3CeX$ or $(C_9H_7)_2CeX_2$ with X = H, BH_4, Cl, N_3, CN, NCO, NCS, NO_2, NO_3, OR, O_2CR, SR, NH_2, alkyl or aryl, whose existence likewise remains unproven, should only be remarked upon in passing[207].

The only organocerium(IV) compound whose existence still appears plausible is the pyrophoric and amazingly water-stable $(C_8H_8)_2Ce$ **200d**. It has been obtained by reaction of $Ce(O-i-C_3H_7)_4$ with triethylaluminum in excess cyclooctatetraene. Its ^{1}H-NMR spectrum shows only one sharp signal at $\delta = 5.6$. The X-ray structure data, which are said to prove a uranocene-like sandwich structure for **200d**, have so far not been published. Reduction of **200d** with alkali metals furnishes the anion $[Ce(C_8H_8)_2]^{2\ominus}$ **201d**[103].

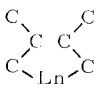
5. Organometallic Compounds with Lanthanoids in the Oxidation State Zero

Typical ligands for organometallic compounds of the transition metals in lower oxidation states are CO and olefins. There has therefore been no lack of attempts to synthesize such carbonyl and olefinic complexes with elements of the third subgroup and the lanthanoids. Whereas carbonyllanthanoid compounds have so far only been detected in a matrix[208], evidence has been obtained for the existence of olefinic complexes in the free state.

Thus, the cocondensation of La, Nd, Sm, or Er with butadiene or 2,3-dimethylbutadiene at 77 K affords brown solids, which, on extraction with toluene or THF, yield paramagnetic compounds for which the formulas **219**, **220** and **221** are under discussion (H atoms not shown)[209].



219



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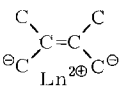


221

Samarium, erbium and ytterbium also react with ethene, propene or 1,2-propadiene at 77 K with formation of orange to black products, the hydrolytic decomposition of which affords the hydrocarbons methane, ethane, propene, propane, butene, butane, allene, or propyne. However, the only compound to have been isolated and characterized is the erbium complex $(CH_3CH{=}CH_2)_3Er$ **222o**[210]. The cocondensation of Sm, Er, or Yb with 3-hexyne at 77 K yields brown solids which upon extraction give the isolable complexes $C_6H_{10}Sm$, $C_{18}H_{30}Er_2$, or $C_6H_{10}Yb$. The structure of these compounds, which are useful as hydrogenation catalysts, is still unknown[133,211].

6. Reactive Behavior and Application in Catalysis and Organic Synthesis

Organolanthanoid compounds, most of which are highly reactive, count among the most novel and versatile tools in the chemist's armamentarium.

A systematic investigation of the chemical behavior of these compounds has not yet been possible, since, in most cases, the synthesis and characterization of the compounds themselves still raise difficulties. On the basis of the studies carried out so far, however, it can be assumed that these compounds should provide interesting new possibilities in catalysis and organic syntheses.

The first indication of the catalytic ability of the organolanthanoid compounds was provided by the observation that oxides, halides, and alkoxides of almost all lanthanoids in the presence of alkylaluminum, alkyllithium, or other organometallic compounds catalyze cracking reactions, oligomerizations, and polymerizations[11,212]. **4h** catalyzes the dimerization of diphenylacetylene[213]; several alkyl(dicyclopentadienyl)lanthanoid[214,215], cyclooctatetraenylcerium, and allyllanthanoid complexes[212] catalyze the polymerization of olefins such as ethene or butadiene.

Initial studies on the reaction of **64r** with propene, which reveal an insertion-elimination equilibrium, provide an insight into the mechanism of such catalytic reactions[82,83].

$$(C_5Me_5)_2LuCH_3 + CH_2{=}CHCH_3 \rightleftharpoons (C_5Me_5)_2LuCH_2CH(CH_3)_2$$
64r

Organolanthanoid hydrides[135,140,210,216], cyclopentadienylytterbium(II) derivatives[182], as well as the cocondensation products of lanthanoids with alkynes[133,211,217] catalyze the hydrogenation of alkenes and alkynes.

Organocerium compounds, which are generated in situ from CeI_3 and alkyllithium, convert ketones into tertiary alcohols in high yields at $-65\,^{\circ}C$. At $0\,^{\circ}C$, an additional reductive coupling is observed[218]. Organocerium compounds are also useful for the synthesis of allyl alcohols[219] and pinacols[220], for aldol reactions with ketones or sterically crowded aldehydes[221], and for the reduction of alkynes and mono- or disubstituted alkenes[222]. These investigations show that organolanthanoid compounds are sometimes helpful in solving chemical problems which cannot be resolved with organic derivatives of main group elements or with transition metal compounds[223].

The homoleptic methyl derivatives **114** methylate α,β-unsaturated aldehydes and ketones in yields of more than 80%, the formation of 1,2-adducts being favored[129].

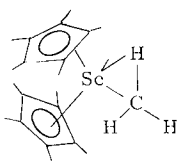
The organolanthanoids are particularly efficient at activating C–H bonds. The compounds **64b**, **64r** (R = CH_3) and **65b**, **65r** (R = H) even cleave the C–H bonds in methane, benzene and tetramethylsilane. By using ^{13}C-labeled methane it was possible to prove that the first step in the substitution reaction is the following exchange reaction, suggesting intermediate formation of the transition state **223r**[85].

$$(C_5Me_5)_2LnR + {}^{13}CH_4 \rightleftharpoons (C_5Me_5)_2Ln{-}{}^{13}CH_3 + RH$$
64b, **r**, **65b**, **r**

$$(C_5Me_5)_2LuCH_3 \underset{-CH_4}{\overset{+CH_4}{\rightleftharpoons}} (C_5Me_5)_2Lu\begin{matrix}CH_3\\ \diagdown\\ \diagup\\ CH_3\end{matrix}\!\!\cdots H$$
64r **223r**

$$(C_5Me_5)_2LuCH_3 + C_6H_6 \longrightarrow (C_5Me_5)_2LuC_6H_5 + CH_4$$
64r **66r**

The most recent investigations show that **64a** also has the ability to activate methane. The "agostic"[224] methyl group is said to be the active center of this compound[225].



64a

The reaction of **53r** with CO in THF, which yields the acyl complex **158r**, proves that even CO is activated by organolanthanoid compounds[154] (see Section 2.9.1).

7. Outlook

The synthesis of a respectable number of organometallic compounds of all the lanthanoids in the last 15 years has filled—albeit tentatively—one of the largest remaining gaps in organometallic chemistry. The fundamental prerequisites for this development have been the easier accessibility of "elemental pure" lanthanoids, the improvements of methods of preparation, and, in particular, the better opportunities for carrying out exact structure determinations within a short time.

Even today, the major concern in this area of chemistry is the problematical and often very troublesome synthesis and characterization of the compounds themselves. However, in the near future, it should be possible to answer at least some of the many questions which are posing themselves as more and more progress is being made regarding the chemistry of organolanthanoid compounds. Some of these questions are: How does the stability of homologous compounds change in going from scandium to lutetium? Are organocerium(IV) compounds able to exist? Is it possible to isolate definite carbonyl, phosphane, or olefinic complexes of the lanthanoids? Is it possible to synthesize organolanthanoid compounds containing lanthanoid-lanthanoid bonds? How useful are organolanthanoid compounds in organic synthesis? Will the organolanthanoid compounds—because of the nontoxicity of their hard-acid lanthanoid ions—oust the ecologically objectionable heavy metal compounds from some fields of application? And last, but not least, is this sector of organometallic chemistry not a real bonanza for theorists?

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Mycotoxins from Mold Fungi—Weapons of Uninivited Fellow-Boarders of Man and Animal: Structures, Biological Activity, Biosynthesis, and Precautions**

By Burchard Franck*

In addition to the antibiotics, mycotoxins represent a second large group of biologically active substances of microbial origin. Over 300 mycotoxins are so far known and can be subdivided into 25 structural types. They are formed by approximately 350 molds of which there are 10000 different strains. As mycotoxin-producing molds tend to spread aggressively on foodstuffs, they can cause epidemic mycotoxicoses.—The mycotoxins have been isolated, their structures determined, and their biological activities investigated; their biosynthesis has now also largely been elucidated. Accordingly, mycotoxins are derived from only three groups of key biogenetic building blocks: polyketides, isopentenyl pyrophosphate, and amino acids. Mycotoxins are mainly non-polar, chemically stable, are formed in high concentrations, and do not contain—unlike antibiotics—any sugars. Mycotoxins display an enormous variety of toxic-pharmacological activities, e.g. liver degradation, hemorrhages, carcinomas. The identification of mycotoxicoses is impeded by their long incubation periods and the fact that the mycotoxins tend to accumulate in the mammalian organism, which means that even very low concentrations in food are a potential danger. The particularly dangerous aflatoxin B_1 **1** may not exceed a limit in food of 5 ppb (5 μg/kg), which is difficult to control.

1. Introduction

Everyone knows what happens when fruit juice is left to stand unprotected for a few days (Fig. 1). Mold colonies are formed from the germs present in the air, usually Aspergillus and Penicillium species. We then do not feel like drinking the juice, our instinct warns us to be careful, and this is important because many of these fungi produce poisonous metabolic products which are dangerous for man and mammals. These poisonous substances are called mycotoxins.

The biological activities of the mycotoxins differ from those of the antibiotics produced against bacteria. The mycotoxins and antibiotics provide the microorganisms with effective means of driving other living organisms away from their sources of food. In Figure 1 the molds have already won this battle, as man can now no longer enjoy the foodstuff they have covered.

Some typical features of mycotoxins and antibiotics are compiled in Table 1. Mycotoxins are synthesized by the rapidly growing, aggressively spreading molds; antibiotics are mostly formed by Streptomycetes. Whereas the Streptomycetes are satisfied with residual substances such as cellulose and chitin, which are difficult to degrade, molds compete with higher organisms for their foodstuffs and fodder. Man and mammals are thus greatly endangered by mycotoxins.

Penicillin G and streptomycin are the most important antibiotics, whilst aflatoxin B_1 **1** is the most dangerous representative of the mycotoxins.

The danger posed by the mycotoxins and the diseases they cause, *mycotoxicoses*, were underestimated for a long time, which is why they are also referred to as the "neglected diseases"[1]. This situation changed suddenly from 1960 onwards with the epoch-making discovery of the

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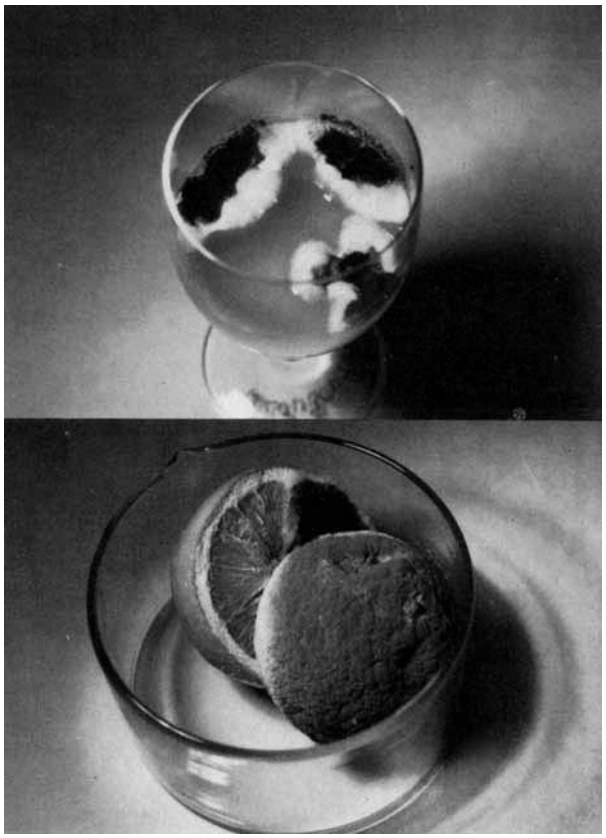


Fig. 1. *Aspergillus niger* growing on orange juice (above) and a mixed infection of Aspergillus and Penicillium species on an orange (below).

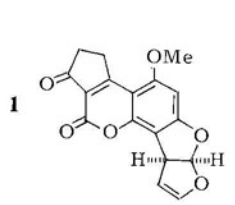
mass poisoning of young turkeys by moldy peanut fodder on farms in South and East England[2,3]. The peanut meal was infected with the mold *Aspergillus flavus*, which produces aflatoxins that are highly toxic (for man as well), causing liver cancer[3]. Since then, intensive interdisciplinary studies have demonstrated that further mycotoxins are responsible for dangerous illnesses. As a result the physiological, toxicological, and food-chemical classification of mycotoxins progressed rapidly[4–11]. Many unpredictable findings were made which had a stimulating influence on large areas of bioorganic chemistry. Three main aspects and important research targets can be distinguished and are dealt with here: 1) Structures and biological activity, 2) biosynthesis of the mycotoxins, 3) protection against their toxic effects.

Table 1. Comparison of mycotoxins and antibiotics.

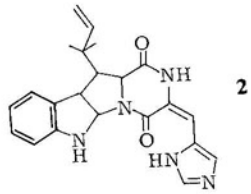
	Mycotoxins	Antibiotics
Active against:	Higher organisms (e.g. mammals)	Bacteria (e.g. pathogenic bact.)
Produced predominantly by:	Molds	Streptomycetes
Preferred nutrient media:	Easy to degrade (e.g. foodstuffs)	Difficult to degrade (e.g. cellulose, chitin)
Typical examples	Aflatoxin B_1 1	Streptomycin, penicillin G

2. State of Development of Mycotoxin Research

More than 300 mycotoxins are so far known and can be subdivided into 25 structural types[4]; they are synthesized by 350 different molds, each of which has up to 100 strains. A total of approximately 10000 mycotoxin producers thus threaten our foodstuffs. This still represents, however, a modest start comparable to the state of antibiotic research 30 years ago[12].



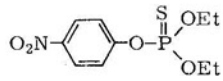
Aflatoxin B_1[3,14]
(Aspergillus flavus)
LD_{50} (OR, rat) 7.2 mg/kg[4]



Roquefortin[15,16]
(Penicillium roqueforti)
LD_{50} (IP, mouse) 10–20 mg/kg[4]

As_2O_3

Arsenic
LD_{50} (OR, rat) 15 mg/kg[13]



Parathion (E 605)
LD_{50} (OR, rat) 4–13 mg/kg[13]

Fig. 2. Structures and toxicities of two typical mycotoxins and comparable toxins. (OR = oral, IP = intraperitoneal administration).

Figure 2 shows two typical mycotoxins, aflatoxin B_1 **1**[3,14] and roquefortin **2**[15,16]. The toxicities of two well-known poisons, arsenic and parathion, are also given for comparison. The roquefortin-producing mold *Penicillium roqueforti* is used in the preparation of many types of blue cheeses. Mycotoxins are thus not only limited to those molds which occur as avoidable infections of foodstuffs. Fortunately, the roquefortin content of normal blue cheeses is so low (<7 ppm)[17] that the lethal adult dose is only reached after eating 200 kg of the cheese.

Mycotoxins with more than twenty different activities (see Table 5) can be isolated from the molds found in human food; they are often threatening to life and many of them cause cancer[4,6]. According to an estimate of the International Agency on Cancer[18], 80% of cancers are caused by environmental factors, mycotoxins making a considerable contribution to this.

Practically all foodstuffs may contain toxin-producing molds. The mycotoxin contents of the majority of the foodstuffs listed in Table 2 are checked continuously in many countries.

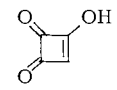
Table 2. Foodstuffs particularly threatened by mycotoxin-producing molds.

Nuts	Cereal products	Fruit products	Foodstuffs of animal origin
Peanuts	Rice	Tomato juice	Milk
Brazil nuts	Maize	Apple juice	Cheese
Walnuts	Rye	Orange juice	Egg products
Hazelnuts	Wheat	Wine	Sausage meats
Almonds	Soybeans	Fruit purees	Liver
Pistachio nuts	Cornflakes	Fruit jellies	Kidney

Man is threatened in two ways by mycotoxins. First of all directly by the consumption of foodstuffs which are infected with toxin-producing molds. Secondly in an indirect manner by the meat, milk, and eggs of animals whose fodder contained mold colonies (carry-over) due to the high persistence of the mycotoxins in metabolism. This applies especially to liver and kidney, where mycotoxins can be accumulated[19].

3. Structures, Biological Activity, and Mycotoxicoses

As is typical for natural products of secondary metabolism, mycotoxins mainly occur as groups of structurally related compounds containing numerous components, many of which are regioisomers, diastereomers, or enantiomers. The mycotoxins also display a wide variety of structures and chemical properties. This is demonstrated, for example, by the readily water-soluble, highly toxic moniliformin **3**[20] from *Fusarium moniliforme* and the complex, hydrophobic, tremorgenic penitreme A **4** from *Penicillium crustosum*[21,22]. The isolation and purification of mycotoxins thus require intensive use of the most modern separation methods[23].



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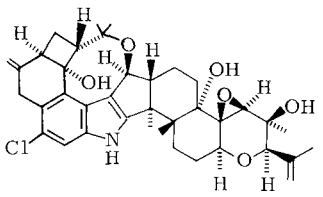

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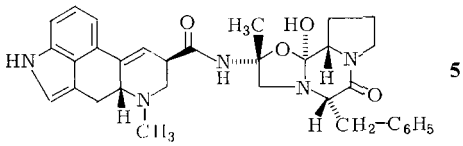
3.1. Ergotism

The structural elucidation of the mycotoxins began with the causative agent of the longest known mycotoxicosis, *ergotism*. This disease is caused by the filamentous fungus *Claciceps purpurea*, which is to be found on ears of grain where it forms the black sclerotia known as ergot[24]. These found their way into the bread cereals and caused epidemic, mass poisoning which has been known in Europe since the Middle Ages[25,26]. Chemical investigations performed for well over one hundred years finally led to the elucidation of two mycotoxin groups—the ergot alkaloids[27] (e.g., ergotamine **5**) and the yellow ergochromes[28] (e.g., secalonic acid A **6**) (Fig. 3).

The mycotoxicosis ergotism is associated with burning pains in the extremities and was previously called St. Anthony's fire. Pilgrimages to the grave of St. Anthony in Padua indeed often resulted in the ergotism being cured since the afflicted persons had left the area where the bread was contaminated with ergot[29].

The fact that the action of ergot involves not only the long-known ergot alkaloids[27] but also the more toxic ergochromes[28,30,31], which are present in larger quantities[32], was appreciated at a relatively late stage after the structure of this new group of natural products had been established. This is because the ergochromes possess six to ten centers of chirality, and thus mixtures of diastereomers occur which could only be separated by modern chromatographic methods. Between 1964 and 1966 our group purified nine sterically uniform ergochromes and determined their structures, including the absolute configurations at a



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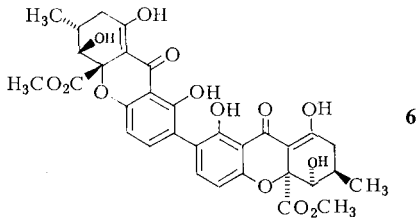
Ergotamine
LD_{50} (IV, mouse) 62 mg/kg[13]
peripheral vascoconstriction, gangrene,
and necrosis of the extremities[27]

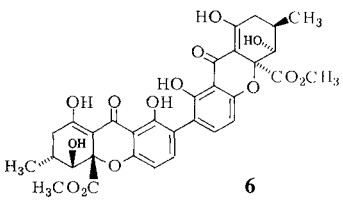


6

Secalonic acid A
LD_{50} (IV, mouse) <50 mg/kg[31]
liver necrosis

Fig. 3. Ergotism: causative agents and their modes of action. IV = intravenous administration.

total of 78 centers of chirality[33-35]. The studies of other groups of workers produced a further five ergochromes[36]. *Steyn*[37] in Pretoria made a surprising discovery when he isolated an enantiomer of secalonic acid A **6**, the secalonic acid D **7**, as the toxic principle of the maize fungus *Penicillium oxalicum*. **7** possesses the opposite configurations to those of **6** at all six of its centers of chirality (Fig. 4). This



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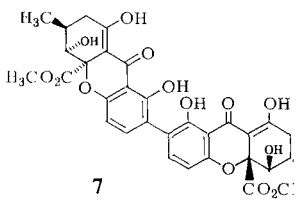

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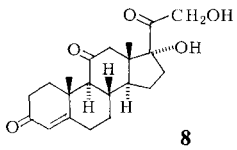

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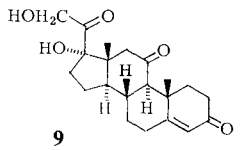

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Fig. 4. Enantiomeric ergochromes and steroids. Secalonic acids A **6** and D **7** occur in nature; the enantiomer **9** of cortisone is not a natural product. The broken line is the mirror plane.

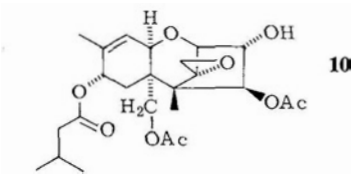
unique finding is as remarkable as if the enantiomer **9** of a steroid hormone (e.g., cortisone **8**) had been isolated as a natural compound.

3.2. Alimentary Toxic Aleukia (ATA)

Alimentary toxic aleukia (ATA) is another serious mycotoxicosis which is caused by a mold growing on cereals[38]. This disease is characterized by progressive damage of the hemopoietic system, which is responsible for the formation of the red and white blood corpuscles. ATA begins with destruction of the skin, hemorrhaging, inflammation, and sepsis (Fig. 5). In the terminal stages the bone marrow atrophies, and the leukocytes and erythrocytes decrease markedly. The mortality of this mycotoxicosis is 60%.

Fig. 5. Initial stage of alimentary toxic aleukia (ATA) in a 15 year old boy (from [41a]).

ATA was identified as a mycotoxicosis as a result of studies on a widespread outbreak of the disease in 1944 in the southern Ural region of Russia which extended over 500 km. The food cereals were infected with toxigenic Fusaria species which synthesize type "T-2 toxin" **10**[39] mycotoxins (Fig. 6).



10

T-2 toxin[39]

(Fusarium culmorum)

hemorrhaging, sepsis, decrease in red and white blood corpuscles,

bone marrow atrophy,

inhibition of protein synthesis (similar to the alkylating agents such as nitrogen mustard gas), damage to the hemopoietic system[4,38].

Fig. 6. Alimentary toxic aleukia: causative agent, its origin and mode of action.

The T-2 toxin **10** inhibits protein synthesis by a mechanism similar to that of nitrogen mustard gas. Since the first representative of this group of mycotoxins was isolated by *Freeman* and *Morrison*[39b] from *Trichothecium roseum*, they were called the "trichothecenes". The more than 50 trichothecenes so far known constitute one of the most important groups of mycotoxins[40]. If there are bottlenecks in the purity control and supply of foodstuffs, especially in tropical climates, the mycotoxicosis ATA caused by the trichothecenes represents a considerable source of danger to the population; this is apparently now the case in Cambodia[41].

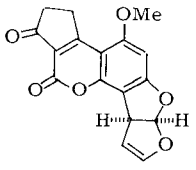
3.3. Aflatoxicosis

Aflatoxicosis was the third epidemic mycotoxicosis to be recognized after ergotism and ATA, and is the most dangerous. As soon as the aflatoxins of the mold *Aspergillus flavus* had been identified as the cause of the "turkey X disease"[2,3], intensive studies were undertaken to establish whether these highly active mycotoxins were also responsible for human mycotoxicoses[42,43]. This required a complicated, comprehensive screening program. For example, the daily consumption of aflatoxins was determined by analyzing a large number of food samples collected from markets and domestic households[44]. A significant statistical relationship between the incidence of liver cancer and the intake of aflatoxins was established. Some typical examples are compiled in Table 3.

Table 3. Incidence of liver cancer (cases per 100000 people per annum) and aflatoxin intake (ng/kg body weight per day) in Africa and Asia [44].

Region	Incidence of liver cancer	Aflatoxin intake
Kenya—highlands	0.7	3.5
Thailand—Songkhla	2.0	5.0
Swaziland—highlands	2.2	5.1
Kenya—medium altitude	2.9	5.8
Swaziland—medium altitude	4.0	8.9
Kenya—lowlands	4.2	10.0
Thailand—Ratburi	6.0	45.0
Swaziland—lowlands	9.7	43.1
Mozambique—Inhambane	13.0	222.4

The normal incidence of liver cancer is two cases per 100000 people per annum. This frequency was observed in dry highlands where it is relatively simple to keep the mold infection of food and thus their aflatoxin content at a low level. The daily aflatoxin intake in these regions is less than 5 ng/kg body weight. If the aflatoxin intake is doubled to 10 ng/kg, as is the case in the more humid lowland areas of Kenya, the average incidence of liver cancer increases by 100%. Although the linear relationship to cancer incidence is not maintained at higher levels of aflatoxin intake, the effect of these mycotoxins is still evident. Similar to the situation in liver cancer, there also seems to be a relationship between aflatoxin intake and the "childhood cirrhosis" encountered in India (Fig. 7)[46].



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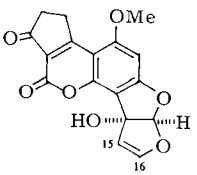
Aflatoxin B_1[3, 14]
(Aspergillus flavus)



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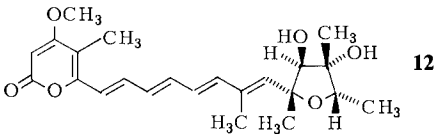
Aflatoxin M_1[45]
(milk from animals whose fodder contains aflatoxin B_1 1)

Fig. 7. Human aflatoxicoses: Causative agents, their origins and modes of action. 1 and 11 cause liver cancer and Indian childhood cirrhosis, respectively. After being converted into the 15,16-epoxides 1 and 11 bind to RNA and other vitally important macromolecules [47].

Of the approximately 20 aflatoxins so far known, special attention should be paid to aflatoxin B_1 1 and the equally carcinogenic aflatoxin M_1 11; the latter is a hydroxylation product formed in the metabolism of mammals whose food contains 1. Aflatoxin M_1 11 in cows' milk may be the cause of severe liver cirrhosis observed in young children in India and Africa. The mechanism of action of the aflatoxins, which includes a 15,16-epoxide and involves cytochrome P-450, is currently under intensive investigation[47,48].

3.4. "Cardiac Beriberi"

A fourth mycotoxicosis is caused by a toxin of the East Asian rice fungus *Penicillium citreoviride*[49], the polyene lactone citreoviridin **12**[50] (Fig. 8). This mycotoxicosis is



12

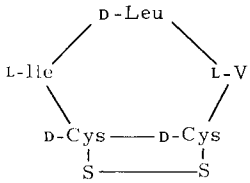
Citreoviridin
(*Penicillium citreoviride*[50]. *Aspergillus terreus*[51])
cardiovascular disorders,
difficulties in breathing with nausea
and vomiting, respiratory arrest[49],
inhibition of mitochondrial ATP synthesis[52].

Fig. 8. "Cardiac beriberi": Causative agent, its origin and mode of action.

referred to as "cardiac beriberi" because its symptoms resemble those of the avitaminosis beriberi which results from a deficiency of vitamin B_1. The disease begins with disturbances of cardiac function and progresses with difficulty in breathing (dyspnea), nausea, and vomiting. Cardiac beriberi was endemic among the rice-eating population of South East Asia until its cause was identified and largely eliminated by preventing fungal infection of rice. Previously, for example in 1908[48], more than 10000 deaths from "cardiac beriberi" were registered annually in Japan alone. Under certain conditions the action of citreoviridin, which evidently[52] involves inhibition of mitochondrial ATP synthesis, can be overcome by administration of vitamin B_1[49].

Until recently it was assumed that citreoviridin **12** was only to be found in the South East Asian rice fungus; in 1980 we discovered[51], however, that this dangerous mycotoxin and two new structurally related mycotoxins are also produced by the mold *Aspergillus terreus* which occurs in soil, on cereals, and sugar-containing foodstuffs. The citreoviridin contents of *A. terreus* reach extremely high levels—up to 2% of the dry mycelium weight.

The finding that *Aspergillus terreus* synthesizes mycotoxins is also important because this mold is used for the biotechnological production of, for example, itaconic acid[53,54]. As is the case with other "useful molds" which simultaneously form mycotoxins, the useful product must be purified with particular care. This also applies to the mold *Aspergillus niger* employed to obtain citric acid[54]; it synthesizes a group of toxic cyclopeptides, e.g. the stereochemically interesting malformin A_1 **13**[55].



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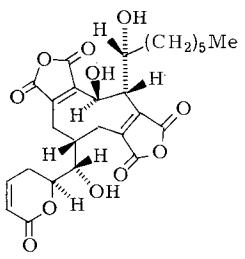
Malformin A_1 [55] *(Aspergillus niger)*: LD_{50} (IP, mouse) 3.1 mg/kg [4, 55].

3.5. Other Mycotoxicoses

In addition to those mycotoxins which are known to be responsible for epidemic mycotoxicoses, due attention should be paid to other identified and not yet identified mold toxins. On account of their special structures and dangerous biological activities (see Table 5), rubratoxin B **14**[56], islanditoxin **15**[57], PR toxin **16**[58,59], and cytochalasin E **17**[60] (Abu = 2-aminobutyric acid) should be mentioned.



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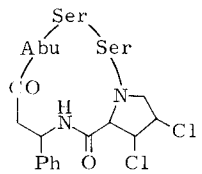

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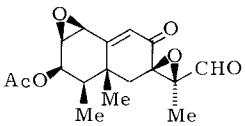

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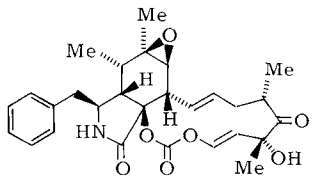

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4. Criteria for the Effectiveness of the Mycotoxins

It would be desirable to classify the mycotoxins so far studied according to their biological activities. On closer consideration, however, this is not so simple because a variety of criteria have to be taken into account (Table 4).

Table 4. Criteria for evaluating the biological activity of mycotoxins.

1) Acute toxicity (LD_{50})
2) Specific pharmacological actions
3) Carcinogenic and mutagenic actions
4) Accumulative effects
5) Aggressiveness of the mold producing the mycotoxin
6) Cause of mycotoxicoses

The acute toxicity is undoubtedly very informative for evaluating a mycotoxin. However, the toxic effects of the mycotoxins commence at levels far below their lethal concentrations, so that their dangerous potency is primarily determined by the nature of their pharmacological actions. The way in which the LD_{50} is determined is also of importance. Somewhat lower toxicities are generally found for oral administration (OR), which is particularly informative for mycotoxins, than for intraperitoneal (IP), intravenous (IV), or subcutaneous (SC) testing. Despite this, listing the mycotoxins in the order of their acute toxicities (as shown in Table 5 for 18 of the mycotoxins discussed in this article) provides a useful guide.

The carcinogenic and mutagenic effects of the mycotoxins are other criteria of their biological activity which cannot be inferred from their acute toxicities. Furthermore, a mycotoxin which can accumulate at sensitive sites in the organism may be much more dangerous on a long term basis than would be expected from its possibly low toxicity. The production of mycotoxicoses is of particular importance. This depends on additional factors such as the ability of the mold synthesizing the mycotoxin in question to spread aggressively on foodstuffs. The mycotoxins ergotamine **5** and secalonic acid A **6** of the ergot fungus *Claviceps purpurea* are typical examples. Although their acute toxicities are comparatively low, they are responsible for the devastating mycotoxicosis ergotism which terrorized the population of Europe for many centuries. Finally, the biological activities of the mycotoxins should not be regarded as being solely of negative value.

In appropriate doses, some mycotoxins have therefore found useful medicinal and other applications. Under the name Gynergen®, the tartrate of ergotamine **5** is used in obstetrics and, because of its α-blocking, vascoconstrictive action, as a remedy for migraine[97]. As indicated by Japanese patent applications, ergochromes formed by ergot fungi and other mold fungi, e.g. the secalonic acids A **6** and D **7**, are being tested as antineoplastic agents. According to the particularly extensive, most recent application[98], secalonic acid derivatives with phthalimidomethyl and maleimidomethyl groups in the 4,4′-position exert antineoplastic activity. One of these derivatives was able, e.g. to increase the survival rate of mice implanted with Ehrlich ascites tumor by over 300%.

Zearalenone **32**, which, despite low acute toxicity, is classed with the mycotoxins, is used in animal husbandry because of its estrogenic and anabolic effects[99, 100]. The compound can markedly accelerate the increase in weight of young animals. A commercially available mixture of epimeric zearalenols prepared from **32** (Ralgro®) produces, e.g. as a 12 mg implant in lambs, a weight increase of ca. 23% and reduces the amount of feeding required. Because of its high persistence and carry-over into meat, this use of zearalone, which gives rise to concern, is difficult to control since both dosage and detection sensitivity (Table 8) are low.

5. Biosynthesis

The mold mycotoxins are secondary metabolic products which have many novel structures and thus provide a wealth of information about the biosynthesis of natural products[61]. This has improved the understanding both of metabolic relationships and of the functions of the key biosynthetic building blocks[62]. This in turn, opens up ways of performing simple biomimetic syntheses for organic chemistry[63].

Table 5. Origin, structures and biological activities [4] of 18 mycotoxins. (*A.* = *Aspergillus*; *Cl.* = *Claviceps*; *F.* = *Fusarium*; *P.* = *Penicillium*).

Mycotoxin	Typical producer	LD_{50} (mg/kg)	Toxicity [a] R.	M.	C.	Biological activity
Penitrem A **4**	*P. cyclopium*	1.05		IP		Induces tremors
Rubratoxin B **14**	*P. rubrum*	3.0		IP		Anorexia, jaundice
Malformin A_1 **13**	*A. niger*	3.1		IP		Gastrointestinal bleeding, liver and kidney damage
Islanditoxin **15**	*P. islandicum*	3.6		SC		Liver degeneration
Emodin **34**	*P. islandicum*	3.7			OR	Anorexia, diarrhea
T-2 toxin **10** [b]	*F. culmorum*	4	OR			Hemorrhaging, skin necrosis
Moniliformin **3**	*F. moniliformine*	4			OR	Hemorrhaging of the skin, intestinal bleeding
Patulin **29**	*P. patulum*	5		IP		Carcinogenic, mitotic poison, hemorrhaging
PR toxin **16**	*P. roqueforti*	5.8	IP			Lung and kidney edema, liver degeneration
Aflatoxin B_1 **1** [b]	*A. flavus*	7.2	OR			Liver carcinoma
Citreoviridin **12** [b]	*P. citreoviride*	7.5			IP	Cardiovascular disorders, respiratory arrest
Cytochalasin E **17**	*A. clavatus*	9.1	OR			Circulatory collapse, liver necrosis
Roquefortin **2**	*P. roqueforti*	15–20	IP			Atonia, prostration
Ochratoxin A **30**	*A. ochraceus*	22	OR			Weight loss, anorexia
Secalonic acid A **6** [b]	*Cl. purpurea*	50	IP			Liver necrosis
Sterigmatocystin **48**	*A. versicolor*	60	IP			Chronic liver and kidney damage
Ergotamine **5** [b]	*Cl. purpurea*	62	IV			Vasoconstriction, emesis, gangrene
Zearalenone **32**	*F. roseum*	?				Estrogenic, anabolic agent

[a] Test animals: R (rat), M (mouse), C (cockerel); administration: IP (intraperitoneal), SC (subcutaneous), OR (oral), IV (intravenous). [b] Causative agent of a dangerous mycotoxicosis.

5.1. Key Building Blocks of Mycotoxin Biosynthesis

Research into mycotoxin biosynthesis began at a time when the necessary methodology had reached a high level due to the development of efficient labeling syntheses, the availability of stable radioactive isotopes, and modern methods for determining their positions. Furthermore, mold fungi proved to be excellent subjects for biosynthetic experiments because their metabolite production was, by comparison, particularly reliable and reproducible; the enzymes of intact cells were also highly accessible to the labeled precursors.

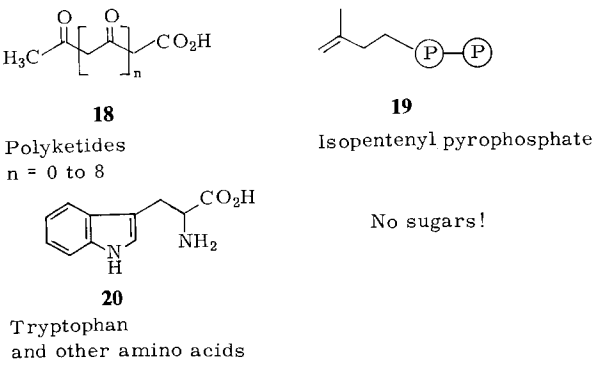


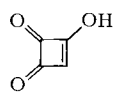
Fig. 9. The most important key building blocks in mycotoxin biosynthesis.

Progress was therefore rapid. The most important result was that the biosyntheses of all 300 known mycotoxins are based on a small number of biogenetic key building blocks, which are summarized in Figure 9. The di- to decaketides **18**, which contain two to ten acetic acid units, are exceedingly important, and mycotoxins with a wide range of biological activities can be constructed from these polyketides in an extremely versatile way. Moreover, many mycotoxins are formed either from isopentenyl pyrophosphate **19**, either alone or in combination with tryptophan **20** and other amino acids.

One of the characteristic features of mycotoxin biosynthesis is that, unlike other products of microbiological origin, e.g. the antibiotics, practically *no sugars* are used as biosynthetic precursors or building blocks.

5.2. Biosynthesis of Moniliformin

Until recently a tetraketide (**18**, n = 2) was held to be the first member of the natural product series formed by the cyclization of polyketides. According to recent labeling experiments performed by our group, however, a diketide (**18**, n = 0) may act as a precursor in the biosynthesis of the structurally particularly simple mycotoxin moniliformin **3**[67].



3

Moniliformin (*Fuarium moniliforme*, *Gibberela fujikuroi*): LD_{50} (OR, cockerel) 4.0 mg/kg [4]: pK_a 0.88 ± 0.03 [66].

The highly acidic moniliformin **3** was first isolated by *Cole* et al.[20] and its structure was elucidated by *Springer* et al.[65]; **3** is formed in high concentrations (up to 33 g/kg[64]) by the mold *Fusarium moniliforme* which is particularly common in maize fodder. This amount would be sufficient to kill 200000 cockerels. *Fusarium moniliforme* and *Gibberella fujikuroi* only produce moniliformin on a solid maize culture medium on which they grow aggressively, transforming it rapidly and completely into a white mycelium.

In order to test the biosynthesis suggested by the structure of moniliformin **3** from a ketide precursor such as **22**, we fed solid cultures of *G. fujikuroi* with [1-^{14}C]-, [2-^{14}C]acetate, and [2-^{14}C]malonate[67]. We also tested another biosynthetic pathway (Fig. 10), and in connection with this

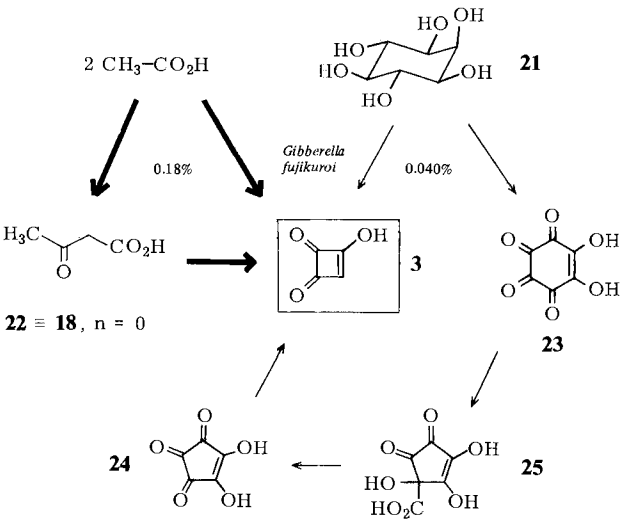


Fig. 10. Biosynthetic pathways and incorporation results for the mycotoxin moniliformin **3**.

checked the incorporation of an additional series of radioactively labeled precursors to rule out the possibility of alternative synthetic routes. Formation of moniliformin from mesoinositol **21** (which is found in many fungal molds) via rhodizonic acid **23** and croconic acid **24** was considered as an alternative biosynthetic pathway. **23** and **24** may be produced by oxidative conversion and benzilic acid rearrangement and are also known natural products. Incorporation experiments with [U-^{14}C]mesoinositol **21** and other precursors, however, only gave very low incorporation levels so that the biosynthetic route via the diketide **22** ≡ **18** (n = 0) seems to be the most likely. The incorporation value of 0.18 for acetate is two orders of magnitude greater than the significance level; this is comparatively high and convincing in view of the many metabolic pathways which require acetate and the fact that the precursors were administered to a solid culture.

The biosynthesis of moniliformin **3** from acetate thus probably proceeds via malonyl coenzyme A **26** and 1,3-butanedione **27** (Fig. 11). Oxidation of the reactive methylene groups of **27** would yield the intermediate described by the tautomeric forms **28a**–**28c**, which could be dehydrated to give moniliformin **3**. Oxidative degradation of radioactive moniliformin **3** obtained after feeding *Gibber-*

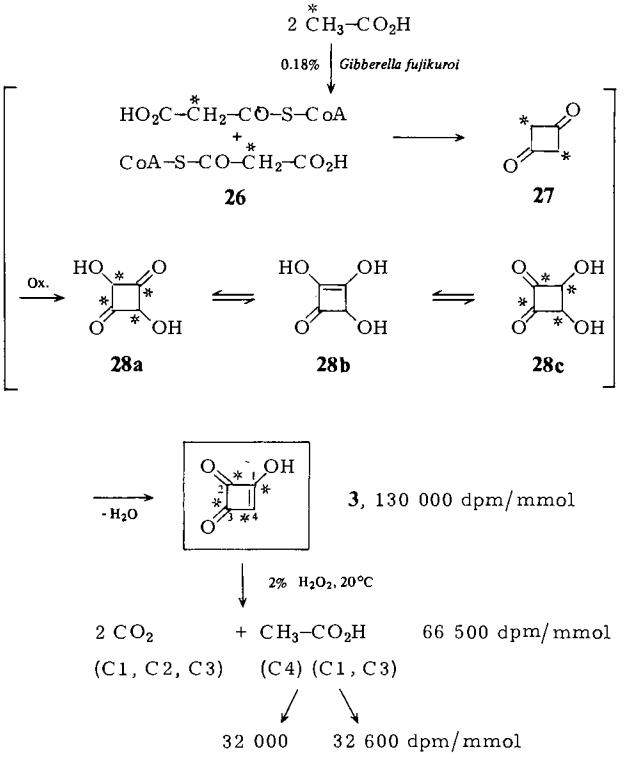


Fig. 11. Formation and degradation of radioactive moniliformin **3** from [2-^{14}C]acetate [67]. dpm = disintegrations per minute *Giberella fujikuroi*.

ella fujikuroi with [2-^{14}C]acetate gave the same specific radioactivities for all the C atoms. This is in accord with the biosynthetic pathway (Fig. 11) involving the tautomeric intermediate **28**.

5.3. Mycotoxins from other Polyketides

Figure 12 summarizes the biosynthesis of two more mycotoxins which are formed from tetra- and pentaketide precursors (**18**, n = 2 and 3, respectively) by consecutive functional changes: the carcinogenic mycotoxin patulin **29** from *Penicillium patulum*[68], which is found in apple juice, and the hepatotoxic ochratoxin **30** from *Aspergillus ochraceus*[69].

The variety of possible condensations undergone, for example, by the nonaketide **31** (≡ **18**, n = 7) is much greater than that of these smaller polyketides. Two bicyclic mycotoxins are shown in Figure 13 as examples; they are derived from two differently folded conformations **31b** and **31c** of the open-chain nonaketide precursor **31a**. These are the polyene mycotoxin citreoviridin **12**, which causes "cardiac beriberi" (Fig. 8), and zearalenone **32**, which has strong estrogenic activity. Incorporation experiments with ^{14}C-labeled acetate and methionine were performed with *Penicillium citreoviride* to clarify the biosynthesis of citreoviridin **12**[70]. These studies demonstrated that the four *C*-methyl groups at positions 4, 12, 14, and 16 are derived from methionine and that some of the chain C atoms are formed from acetic acid; this supports the polyketide concept. After we discovered that citreoviridin **12** is also synthesized in particularly high concentrations by the mold *Aspergillus terreus*, we used this finding for the incorporation of [1-^{13}C]- and [2-^{13}C]acetate and subsequent evaluation by ^{13}C-NMR spectroscopy[51]. Administration of the precursors in the nutrient solution of the mold cultures at the comparatively high concentration of 0.2% gave high incorporation rates of 17.6 and 25.7%, respectively, for the ^{13}C-labeled acetates, thus allowing reliable determination of the position by ^{13}C-NMR spectroscopy.

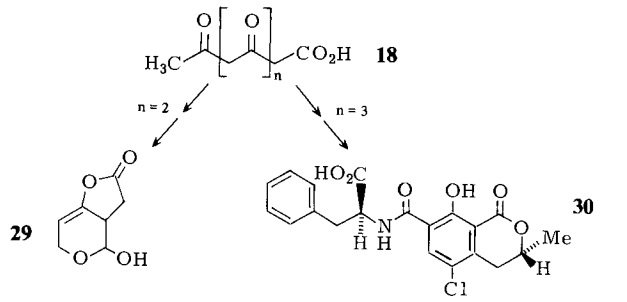


Fig. 12. Polyketide precursors of the mycotoxins patulin **29** and ochratoxin **30** [61].

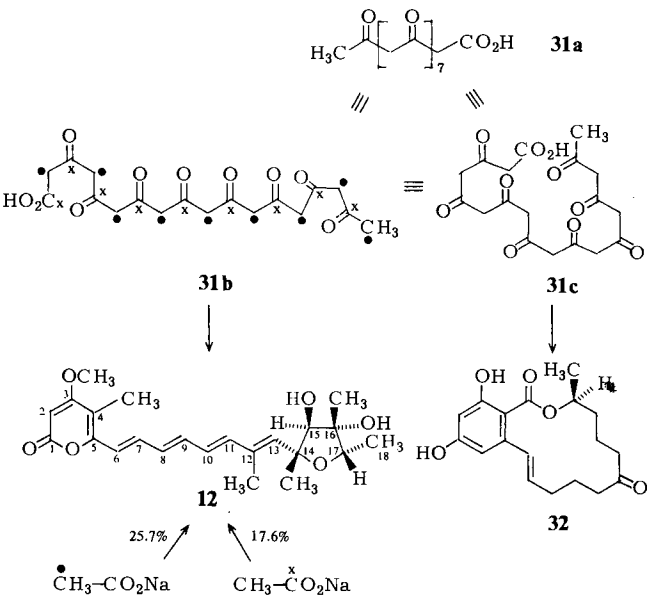


Fig. 13. Biosynthesis of the mycotoxins citreoviridin **12** and zearalenone **32** [72] from the nonaketide **31** (≡ **18**, n = 7). ●, × see text.

According to these studies, all the evenly numbered C atoms (●) of the polyketide chain of the precursor of citreoviridin **31b** are derived from the methyl groups of the acetate building blocks and the unevenly numbered C atoms (×) from the carboxy groups. The C atoms of the *C* methyl and methoxy groups of **12** did not exhibit any significant signals in the ^{13}C-NMR spectrum, which is consistent with their origin in the C_1 pool of the organism. These findings have recently been confirmed in *P. citreoviride*[71].

5.4. Secoanthraquinones

Elucidation of the biosynthesis of mycotoxins of the octaketide type **33**(≡ **18**, n = 6) led to the discovery of previously unknown ring-opening reactions of the anthraquinones (Fig. 14). The toxic emodin **34** of the rice fungus *Penicillium islandicum* is formed from the octaketide **33b**[73] (see Table 5). We were able to prove the hypothesis

that the ergochromes (e.g. secalonic acid A **6**) are produced from an octaketide via **34** shortly after having determined the structure of these mycotoxins[74,75].

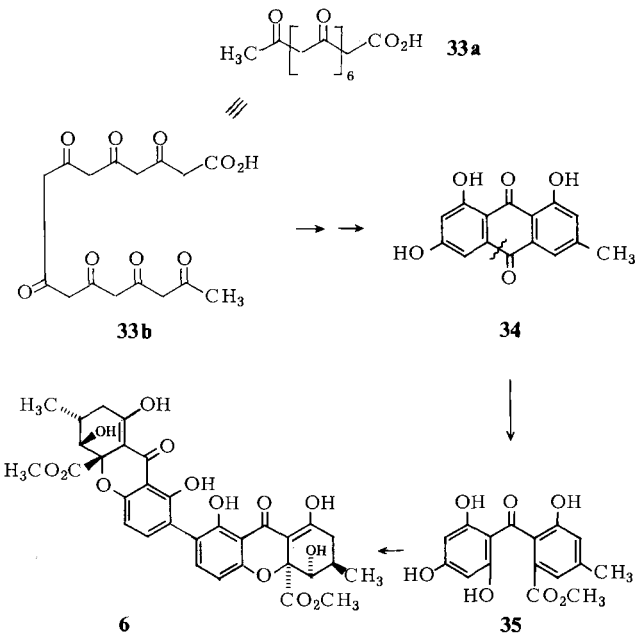


Fig. 14. Biosynthesis of the mycotoxins emodin **34** and secalonic acid A **6** from the octaketide **33** (≡ **18**, n=6).

Oxidative ring-opening of the anthraquinone first yields a benzophenone carboxylic acid **35** which, after functional transformations, cyclizes to the xanthone derivative and finally undergoes oxidative dimerization to give **6**. Figure 15 shows a few of the many incorporation experiments performed to prove the ergochrome biosynthesis[63]. These studies also helped to show whether emodin **34** or emodinanthrone **36** is the better biosynthetic precursor, which was important to explain the ring-opening mechanism.

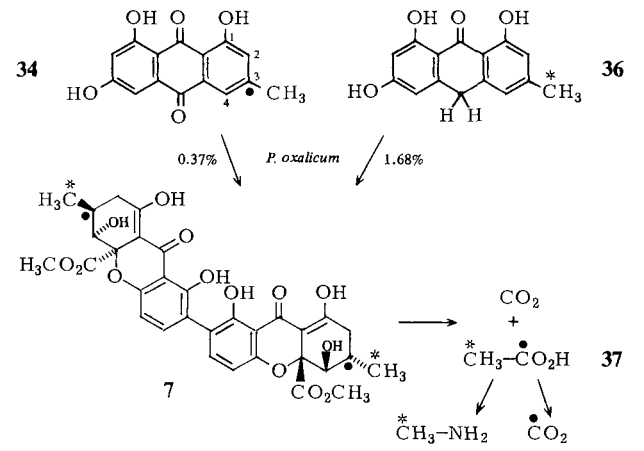


Fig. 15. Incorporation experiments on the biosynthesis of the ergochrome secalonic acid D **7** in the mold *Penicillium oxalicum* [76].

Comparative experiments were carried out to determine the incorporation ratio of emodin **34** and emodinanthrone **36** independent of fluctuations in the growth of the fungal cultures (Fig. 15). For this purpose we prepared emodin **34** and emodinanthrone **36**, labeled with ^{14}C at C-3 and the methyl group, respectively, by total syntheses; a mixture of these compounds was then fed to the mold *Penicillium oxalicum*.

The labeling positions of **34** and **36** were chosen such that their radioactivity could be cleaved from the subsequently isolated biosynthetic product secalonic acid D **7** by Kuhn-Roth oxidation in the form of acetic acid. The desired information about the incorporation values of emodin **34** and emodinanthrone **36** was stored in the respective radioactivities of the carboxy and methyl groups of the "Kuhn-Roth acetic acid" **37**. After Schmidt degradation of the acetic acid to CO_2 and methylamine and oxidation of the latter to CO_2, the incorporation levels were found to be 0.37% and 1.68%, respectively. The radioactivity of the carbon dioxide produced during the Kuhn-Roth oxidation, in addition to the acetic acid, was below the limit of significance. This demonstrated that the ergochrome secalonic acid D **3** is derived directly from two molecules of an anthraquinone by ring opening, whereby emodianthrone **36** proved to be a 4.5-fold better precursor than emodin **34**.

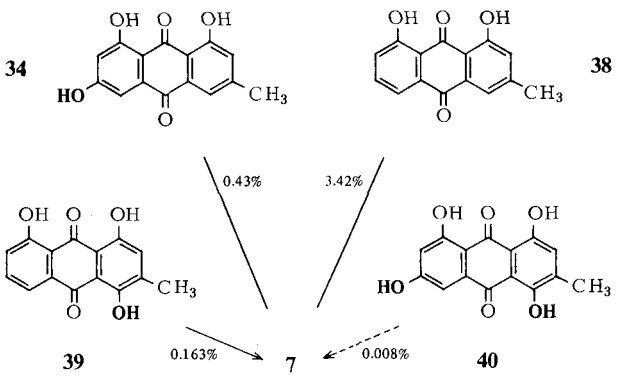
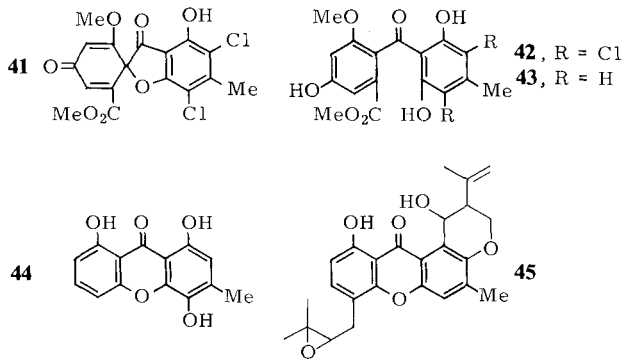


Fig. 16. Competitive incorporation of emodin **34** and three similar anthraquinone precursors **38**—**40** into the ergochrome secalonic acid D **7** in *Penicillium oxalicum* [77].

The incorporation of related anthraquinone natural products **38**—**40** was compared with that of emodin **34** by similar competitive incorporation experiments using natural anthraquinone compounds labeled with different isotopes and *Penicillium oxalicum* (Fig. 16)[63,77]. Chrysophanol **38** was shown to outclass **34** as a biosynthetic precursor of secalonic acid D **7**, whereas islandicin **39**, although its hydroxylation pattern is very similar to that of **37**, was incorporated to a lesser extent. Catenarin **40**, however, could be completely ruled out as a precursor. As is the case in other biosynthetic studies, it is apparent that the synthesis of natural compounds in the organism involves main and subsidiary pathways which combine to produce a *metabolic network* in which the biogenetic *key building blocks* occupy the cross-over points[62,78].

The oxidative ring-opening first discovered by us in 1968 in ergochrome biosynthesis[74,75] demonstrated that the natural anthraquinones are reactive metabolic intermediates. This was subsequently confirmed manifoldly by the fact that other natural products, such as the spirocyclic an-

tibiotic geodin **41**[63,79], the benzophenones dihydrogeodin **42**[79] and sulochrin **43**[80], and the xanthones ravenelin **44**[81] and thajixanthone **45**[82] are derived from anthraquinone precursors and thus form a novel biogenetic group of natural products, the *secoanthraquinones*.



Finally, the impressive studies of several groups of workers on the biosynthesis of the aflatoxins[83] revealed that their basic skeleton is also produced by oxidative ring opening of an anthraquinone precursor (Fig. 17). In this way, the anthraquinone versicolorin A **47** is formed from a decaketide **46** (≡ **18**, n = 8), via its folded conformation **46b**, in a multistep reaction sequence. Oxidative ring opening of **47**, internal rotation of the benzophenone intermediate, and xanthone ring closure yield sterigmatocystin **48**[84,85]. Oxidative transformations at the phenol ring of **48** then furnish the coumarin system of aflatoxin B_1 **1**.

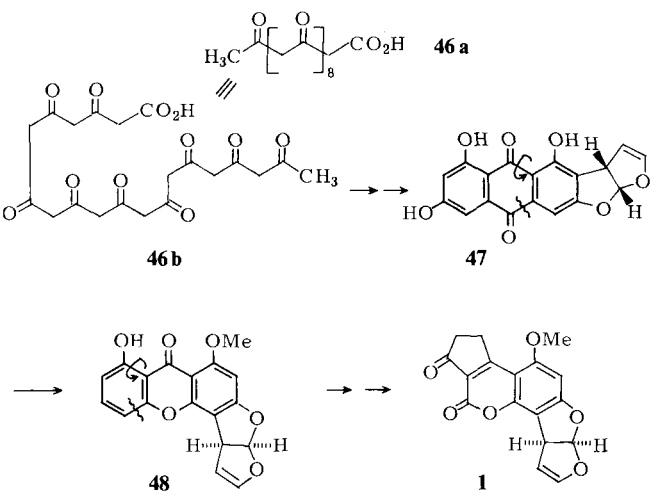


Fig. 17. Biosynthesis of aflatoxin B_1 **1** from the decaketide **46** (≡ **18**, n = 8).

5.5. Isoprenoid Mycotoxins

Compared with mycotoxins derived from polyketides (**18**, n = 0...8), those formed from other biosynthetic precursors are somewhat less important as regards their number and structural diversity, but not their physiological significance. The T-2 toxin **10**[86] from *Fusarium culmorum* and PR toxin **16**[87] from *Penicillium roqueforti*, shown in Figure 18, are two examples of mycotoxins derived from isopentenyl phosphate **19**, the next most common biosynthetic precursor. The biosynthesis of these sesquiterpene mycotoxins, which are constructed from three isoprene building blocks, commences with the differently-folded isomers **50** and **51** of farnesyl pyrophosphate **49**. Enzymatic elimination of the pyrophosphate induces ring closure to give **52** and **54**, respectively[86,87]. This is followed by methyl migration, the introduction of more functional groups, and the formation of the physiologically active epoxide groups to yield T-2 toxin **10** and PR toxin **16**.

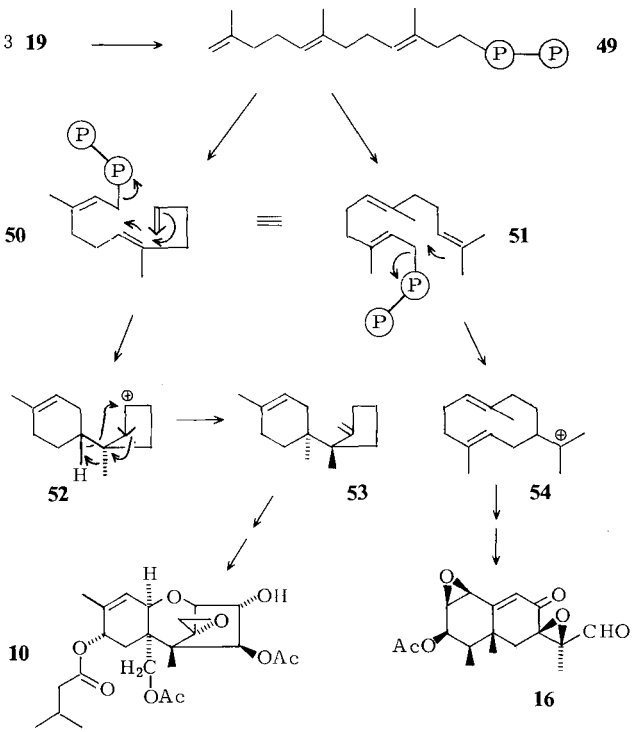


Fig. 18. Biosynthesis of the sesquiterpene mycotoxins T-2 toxin **10** and PR toxin **16** [86, 87].

After the polyketides **18** and isopentenyl pyrophosphate **19**, the third group of mycotoxin biosynthetic building blocks are the amino acids, especially tryptophan **20** (Fig. 9). The usually cyclic peptide mycotoxins (e.g., malformin A_1 **13** or roquefortin **2**) often exhibit lipophilic behavior since they only possess a few polar groups or are substituted with isoprene building blocks (prenyl groups). This represents a further general difference between mycotoxins and antibiotics (Table 1): whereas many antibiotics are readily water-soluble because they are glycosides or possess other polar structures, the mainly nonpolar character[*] of the mycotoxins is further enhanced by prenyl groups which almost appear to be like "antisugars".

Roquefortin **2** from *Penicillium roqueforti* is a typical example of a nonpolar, prenyl-substituted peptide mycotoxin (Fig. 19). The most interesting step in its biosynthesis[80,89] is the introduction of a dimethylallyl group into the diketopiperazine **56**, formed from tryptophan **20** and histidine **55**, coupled to a further ring closure. This may be accounted for, according to analogous chemical reactions[90],

[*] The highly polar mycotoxin moniliformin **3** is an exception.

by the enzymatic introduction of an isopentenyl residue with **19** at the nitrogen or at C-2 of the indole moiety, followed by sigmatropic rearrangement of the isopentenyl residue to C-3 and cyclization of the 3*H*-indole to afford the aminal arrangement of roquefortin **2**.

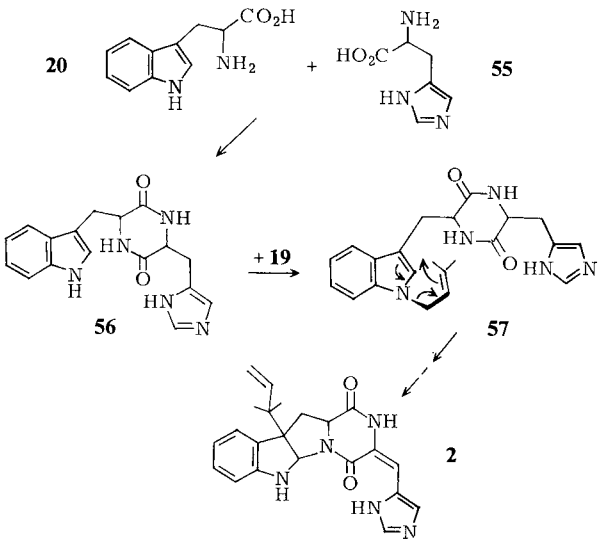


Fig. 19. Building blocks and biosynthetic pathway of roquefortin **2**.

6. Protection against Mycotoxins

An awareness of the causes of mycotoxicoses has led to the development of a wide range of protective measures against mycotoxins in foodstuffs[7] (Table 6).

Table 6. Measures for the prevention and deactivation of mycotoxins in foodstuffs.

1) Protection against toxin-producing molds
2) Culling of infected fruit
3) Chemical deactivation
   - heating
   - UV irradiation
   - oxidizing agents
   - acidification
   - addition of bases
4) Biological deactivation
   - reaction with food constituents
   - passage through domestic livestock and animals for slaughtering
   - degradation by microorganisms
   - interaction with inhibitors in metabolism

The prevention or minimization of toxin-producing molds in foodstuffs and the resulting elimination of mycotoxins are certainly the most important[91]. Compared to this the three other measures involve a great deal of technical effort and entail serious disadvantages such as incompleteness, production of changes in taste, and the possible formation of daughter products which are toxicologically difficult to control. Over the past few years, many countries have laid down limits for the maximum concentrations of the particularly dangerous aflatoxins in foodstuffs (Table 7).

The aflatoxin limiting values cited are based on the state-of-the-art in analytical detection and the so-called

Table 7. Legal control of aflatoxins in 10 countries (state in 1977; according to [92]).

Country	Foodstuff	Aflatoxin limit [μg/kg] [a, b]
Denmark	Peanuts and Brazil nuts	0
Federal Republic of Germany	All foodstuffs	5 B_1
		10 G
France	All foodstuffs	5 B_1
Great Britain	Peanuts	50 B_1
India	Peanut meal	30 B_1
Italy	Peanut products	50 B_1
Japan	All foodstuffs	0
Netherlands	Peanut products	0
Poland	All foodstuffs	0
USA	Peanut products	15 G

[a] B_1 = maximum limit for aflatoxin B_1 **1**. [b] G = maximum limit for the total aflatoxin concentration.

"no effect level" which, according to the evaluation of animal experiments by *Friedmann*[93], corresponds to a daily intake of 9.6×10^{12} molecules per kg body weight = 5 ng/kg.

If it is accepted that a threshold value for carcinogenic activity exists, for aflatoxin B_1 **1** this would be 375 ng for an adult weighing 75 kg. 100 g of food which complies with the limits prescribed by various countries (Table 7) can, however, contain up to 5000 ng aflatoxin B_1 **1**. It is thus evident that the understanding of the threshold value of aflatoxin activity and its analytical control urgently require further development.

A comprehensive review of the methods available for multimycotoxin analysis in foodstuffs has been published by the *"IUPAC Commission on Food Chemistry"*[123]. Accordingly, the analysis of a foodstuff sample, which must amount to at least 25 g, consists of five equally important procedures: extraction, concentration, separation, identification, and quantitative determination. The most important separation methods, usually associated with identification, are thin-layer chromatography, high performance liquid chromatography (HPLC), and FDI mass spectrometry.

Fortunately, the identification method described by *Patterson* and *Roberts*[101], which has proved to be particularly effective, can be used "on the spot" without requiring complicated apparatus. It consists of a combination of two-dimensional, thin-layer chromatography systems on silica gel. Because of its higher sensitivity, the method should be superior to HPLC methods and is distinguished by the fact that it gives the individual mycotoxins good "chromatographic windows". The detection limit varies with the mycotoxin and the foodstuff being investigated (Table 8). Thus, e.g. for aflatoxin B_1 in milk concentrates,

Table 8. Detection limits in ng/kg for mycotoxins in foodstuffs according to *Patterson* and *Roberts* [101].

Foodstuff	Aflatoxin B_1 **1**	Sterigmatocystin **48**	T-2-Toxin **10**	Zearalenone **32**
Peanut flour	100	—	—	—
Maize	100	1000	20000	2000
Wheat	200	1000	20000	2000
Milk concentrate	300	2000	20000	10000

a lowest detection limit of 300 mg/kg has seen found, which corresponds more or less to the "no-effect level".

Somewhat higher aflatoxin limits are allowed for animal fodder (in the FRG 10—50 μg/kg)[94], since the activity of the aflatoxins is calculated to be reduced by a factor of 100 after "carry-over" into the milk and meat of domestic livestock. This is due to excretion of the aflatoxins and their metabolic detoxification. Figure 20 summarizes some of the weakly toxic metabolic products of aflatoxin B_1 **1** which have been detected in animal experiments[4].

It is remarkable that hydroxylation or release of hydroxy groups at the C atoms 5, 8 and 16 considerably reduces the acute toxicity of aflatoxin B_1 **1**; unfortunately, hydroxylation of **1** at C-14 to aflatoxin M_1 **11** in cows' milk hardly decreases its toxicity or tendency to cause liver carcinoma[95,96].

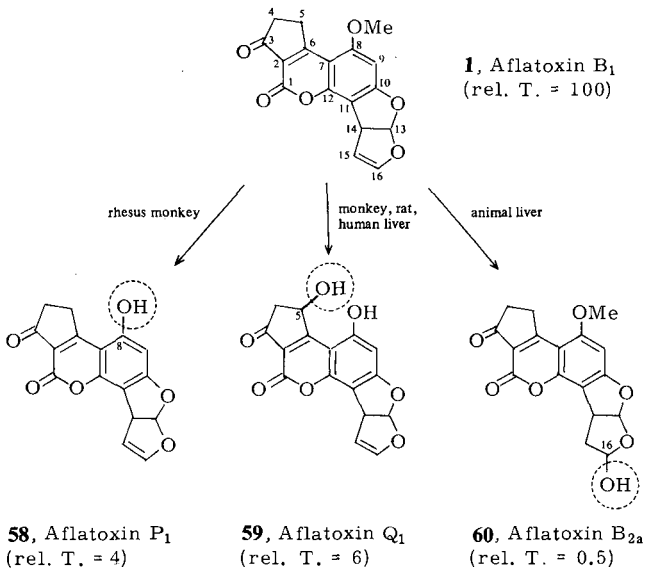


Fig. 20. Structures and relative toxicities (rel. T.) [4] of some metabolites of aflatoxin B_1 **1**. Structural changes are indicated by the broken circles.

7. Outlook

Although research on mycotoxins (e.g. the ergot alkaloids) started before the era of antibiotic chemistry, it has not been pursued with the same intensity until recently. More interest was shown in the medically useful antibiotics. The situation began to change, however, after it was appreciated that, besides the diseases which can be cured by antibiotics, there are many others which can be eliminated by being aware of and preventing mycotoxins.

It should actually be easier to stop molds from infiltrating into food and fodder than to prevent human bacterial infections. This is, however, hindered by the traditional generosity and inexperience we show when dealing with the aggressiveness of food molds. Furthermore, because of their long incubation periods some mycotoxicoses can only be identified by modern statistical methods and did thus only gained importance with the decrease of other diseases and increase of average life expectancy.

I would like to thank my coworkers who are named in the literature published by our group and our microbiologist, Frau Cornelia Peters, for their successful cooperation. The investigations were generously supported by the Landesamt für Forschung in Nordrhein-Westfalen, the Deutsche Forschungsgemeinschaft, and the Fonds der Chemischen Industrie.

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Thin-Layer Chromatographic Enantiomeric Resolution via Ligand Exchange

By *Kurt Günther, Jürgen Martens**, and *Maren Schickedanz*

Today, gas[1] and liquid chromatography[2] are the methods of choice for the resolution of enantiomeric organic compounds in analysis. However, these methods necessitate the use of expensive apparatus and, in part, derivatization of the samples. Chiral amino acids are increasingly gaining importance as building blocks for the preparation of biologically active peptides in asymmetric syntheses[3] and as pharmaca[4]. A simple and rapid method of monitoring optical purity is therefore desirable.

A glass plate covered with hydrophobiated silicic acid (RP 18-TLC) is immersed (1 min) in a 0.25% copper(II) acetate solution (methanol : water = 1 : 9 v/v) and subsequently dried. The plate is then immersed in a 0.8% methanolic solution of the *chiral* selector (1 min). A suitable selector is (2*S*,4*R*,2′*RS*)-4-hydroxy-1-(2′-hydroxydodecyl)-proline **1**[5]. After being allowed to dry in the air, the plate is ready for chromatography.

1

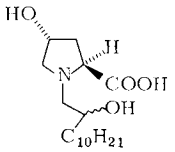

Table 1. Enantiomeric resolution of amino acids by thin layer chromatography [a].

Amino acid	R_f value (configuration)	Eluent [b]
Isoleucine	0.37 (2*R*,3*R*)	A
	0.44 (2*S*,3*S*)	
Phenylalanine	0.38 (*R*)	A
	0.45 (*S*)	
Tyrosine	0.26 (*S*)	B
	0.34 (*R*)	
Tryptophan	0.39 (*R*)	A
	0.45 (*S*)	
Proline	0.40 (*R*)	B
	0.59 (*S*)	
Glutamine	0.37 (*S*)	A
	0.53 (*R*)	
3-Thiazolidine-4-carboxylic acid	0.42 (*S*)	A
	0.52 (*R*)	

[a] Development distance 14 cm. Saturated chamber. [b] A: methanol/water/acetonitrile = 50/50/200 (vvv); B: methanol/water/acetonitrile = 50/50/30 (vvv).

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Using the plates thus impregnated, we have succeeded in performing thin-layer chromatographic enantiomeric resolution via ligand exchange: 2 μL of each of the racemic α-amino acids in Table 1 was applied as a 1% solution to the TLC plates and eluted with the given eluent (30—45 min). After drying, the spots were visualized using 0.1% ninhydrin reagent. The resolution of the enantiomers was so good that the respective antipodes could be determined at trace levels; the lowest level of detection was found to be ≥ 1%, although this value can probably be improved.

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Topological Charge Stabilization and the Equilibrium between P_4S_3 and As_4S_3**

By *Benjamin Gimarc** and *P. J. Joseph*

Recently, *Blachnik* and *Wickel*[1] reported the results of their experimental studies on the equilibrium system P_4S_3/As_4S_3. When the reactants are mixed in the stoichiometric ratio (1 : 3), the equilibrium lies predominantly to the side of PS_3As_3 [eq. (a)].

$$P_4S_3 + 3\,As_4S_3 \rightleftarrows 4\,PS_3As_3 \qquad (a)$$

P_4S_3 and As_4S_3 are cage or end-capped triangular prism structures with a unique apical atom, three equivalent bridging atoms, and three atoms in the equilateral triangular base[2,3]. In these molecules the sulfur atoms occupy the bridging positions, while atoms of the less electronegative group 5B elements are located at apical and basal sites. Presumably the particularly stable equilibrium product PS_3As_3 has a similar structure, with a P atom at the apex, bridging S atoms, and basal As atoms. *Blachnik* and *Wickel* attribute the stability of this product to the greater strength of PS compared to AsS bonds and to the increase in the number of PS bonds from 6 in the educt to 12 in the product PS_3As_3.

We report here an alternative explanation. The stability of PS_3As_3 is a beautiful example of the operation of the rule of "topological charge stabilization"[4]. The $P_7^{3\ominus}$ ion is isoelectronic and isostructural[5] with P_4S_3, As_4S_3, and

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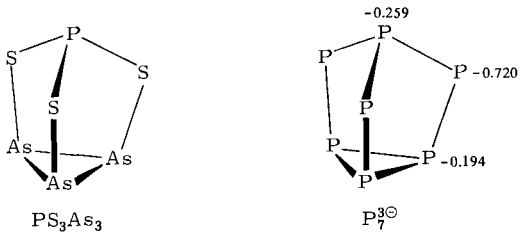
PS_3As_3. Because all the atoms of $P_7^{3\ominus}$ are alike, we call this the uniform reference frame for the end-capped triangular prism structure. The connectivity of atoms and the number of valence electrons cause the three different kinds of atomic positions in $P_7^{3\ominus}$ to have different charge densities, which we calculated using the extended Hückel (EH) method.



PS_3As_3 $P_7^{3\ominus}$

Scheme 1. Structures of PS_3As_3 and $P_7^{3\ominus}$ (charge densities shown).

The largest charge densities are in the bridging positions with smaller densities at apical and basal sites. The rule of topological charge stabilization states that *particularly stable structures result from the substitution of electronegative heteroatoms at sites where electron charges are more negative in the homoatomic, isoelectronic uniform reference frame.* Application of this rule to PS_3As_3 with the charge density distribution in $P_7^{3\ominus}$ (Scheme 1) suggests that in PS_3As_3 the electronegative S atoms should occupy the bridging positions, the less electronegative P atom the apical site, and the still less electronegative As atoms should prefer the basal positions, as confirmed by its structure[6]. The rule of topological charge stabilization has been shown to predict the correct order of relative stabilities for a wide variety of planar, two-dimensional, conjugated molecules[4]. PS_3As_3 is one of a number of examples that demonstrate the operation of this rule for three-dimensional structures[7,8].

Although charge densities obtained from EH calculations are generally regarded as too large, the relative ordering of charges—all that is required for the operation of our rule—is probably reliable. The charge densities in $P_7^{3\ominus}$ were obtained using 3d AOs in the basis set. Without d AOs, but using the extended Hückel, charge-iteration procedure, the same qualitative trend results: the highest charge density is located on the bridges, followed by the apex, and finally by the triangular base. It should be borne in mind that our conclusions depend on the pattern of charges for the homoatomic system that is isoelectronic and isostructural with the heteroatomic system of interest. The unperturbed charge distributions in the homoaromatic reference system may not be the same as those obtained for the heteroatomic structure. For example, *Paddock* et al.[9] report that in P_4S_3 the apical P atom is slightly positive relative to the basal P atoms—opposite of what we find for the homoatomic $P_7^{3\ominus}$ ion. From the heteroatomic results, one would conclude that the most stable product of atomic exchange would be AsS_3P_3 with an apical As atom. But it is the charge distribution in the unperturbed or homoatomic system that determines the first-order perturbation correction to the energy of the heteroatomic analogue[7]. Our concept makes no assumptions about the mechanism that exchanges P and As atoms in the system P_4S_3/As_4S_3 [eq. (a)].

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$[(Me_2N)_2SF_2]^{2\oplus}$, a Sulfur(VI) Dication**

By *Hartmut Henle, Reinhard Hoppenheit,* and *Rüdiger Mews**

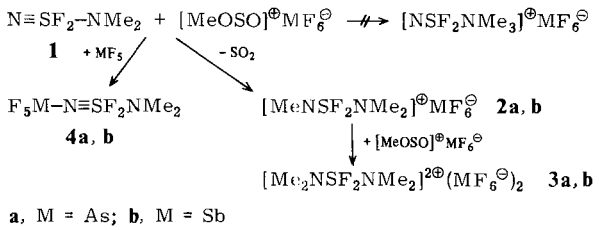
Salts containing sulfur(VI) monocations can be prepared by abstraction of $F^\ominus$ from hexa-[1,2] or pentacoordinated species[3,4], by oxidative addition to S^{IV} derivatives[5], or by addition of cations to species having SN multiple bonds[6]. Similar methods have been developed for the synthesis of sulfur(IV) monocations[3,4,7]; abstraction of $F^\ominus$ from bis(dimethylamino)difluorosulfurane has even led to a sulfur(IV) dication[8].

Alkylation of $N{\equiv}SF_3$ and its derivatives $N{\equiv}SF_2R$ presents a convenient route to sulfur(VI) monocations:

$$N{\equiv}SF_2R + \text{alkyl-OSO}^\oplus MF_6^\ominus \xrightarrow[-SO_2]{} [\text{alkyl-NSF}_2R]^\oplus MF_6^\ominus$$

$R = F$[6a], $NSOF_2$, $CF(CF_3)_2$, $C(CF_3)_3$[6c]

Exclusively the thiazyl nitrogen atom is alkylated, even in the presence of other nucleophilic positions, e.g. a dimethylamino group as in **1**. The synthetic potential of the $MeOSO^\oplus$ cation[9] is convincingly demonstrated by its ability to alkylate even the monocation in **2**. This leads to the salts **3**, which contain the dication $[(Me_2N)_2SF_2]^{2\oplus}$.



a, M = As; **b**, M = Sb

When **1** and $(MeOSO)^\oplus MF_6^\ominus$ are allowed to react in the molar ratio 1:2 in liquid SO_2 at room temperature, salts **3** are formed in quantitative yield[14]. The adducts **4**[10] or the salts **2** of the monocation $[MeNSF_2NMe_2]^\oplus$[11] may occur as impurities.

The course of the reaction indicates how the reactivity of the N≡S triple bond is influenced by substituents bonded to N and S. For the formation of dications the presence of ligands at the nitrogen atom having a +I-effect (such as the methyl group) is necessary; protonation of **1** in the superacid medium HF/AsF_5 leads only to the monocation **5**[14].

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$1 + HF/AsF_5 \longrightarrow [HNSF_2NMe_2]^{\oplus}AsF_6^{\ominus}$ **5**

$NSF_3 + HF/AsF_5 \longrightarrow [F_5S{-}NH_3]^{\oplus}AsF_6^{\ominus}$ **6**

In contrast, NSF_3 reacts with HF/AsF_5 to afford the stable and isolable pentafluorosulfanylammonium salt **6**[12, 14]. The dimethylamino group in **5** reduces the electrophilicity of the central sulfur atom to such an extent that $F^{\ominus}$ can no longer add to increase the coordination number; in this way, all subsequent steps to a product analogous to **6** are blocked.

The salts **3** are stable, colorless solids (m.p. = 101 °C (**3a**), 103 °C (**3b**)) that are readily attacked by nucleophiles, e.g. H_2O or $X^{\ominus}$ of NaCl- and KBr-IR plates. They were characterized by elemental analysis and by IR and NMR spectroscopy (Table 1). Bands at 945 and 910 cm^{-1} in the IR spectrum are assigned to the $\nu_{as}(SF)$ and $\nu_{sym}(SF)$ vibrations.

Table 1. NMR data of salts **3** and **5** [a] as well as the neutral S^{IV} derivative $(Me_2N)_2SF_2$ [13].

	^{19}F [a] $\delta(SF_2)$	^1H $\delta(CH_3)$	^{13}C {b} $\delta(CH_3)$	$^4J_{HF}$ [Hz]	$^3J_{FC}$ [Hz]
3a	38.6 [c]	4.20 (t)	48.19 (t)	4.75	2.1
3b	37.9 [c]	4.22 (t)	48.21 (t)	4.80	2.1
5	54.7 (sept.)	3.16 (t) (N–H 7.37)		2.89	
$(Me_2N)_2SF_2$	7.5 (br. s)	2.72 (br. s)	37.71 (s)	—	—

[a] ^{19}F-NMR (**3a**, **3b**: 60 MHz, SO_2, 301 K; **5**: 75.4 MHz, SO_2, 253 K), ^{13}C-NMR (20.15 MHz, SO_2, 309 K), ^1H-NMR (80.13 MHz, SO_2, 304 K). [b] Proton decoupled. [c] Of the 13 lines expected only 11 were observed.

The NMR data for the cations of salts **3** and **5** as well as the neutral S^{IV} derivative $(Me_2N)_2SF_2$[13] are shown in Table 1; nevertheless, a direct comparison of the cations with the neutral compound is not without problems since in this the sulfur atom has trigonal-bipyramidal coordination, but in the cation the sulfur atom is tetrahedral. The nature of the anion in **3** does not influence the spectroscopic data of the dication; no interaction therefore appears to be present in solution.

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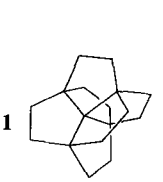
[10] **4a**: ^{19}F-NMR (60 MHz, SO_2, stand. $CFCl_3$): $\delta = 54.75$ (br. s, SF), -33.75 (br. s, AsF); ^1H-NMR (60 MHz, SO_2, stand. TMS): $\delta = 3.47$ (t, $J(HF) = 2.7$ Hz, CH_3); **4b**: ^{19}F-NMR (60 MHz, SO_2, stand. $CFCl_3$): $\delta = 56.97$ (sept., SF); ^1H-NMR (60 MHz, SO_2, stand. TMS): $\delta = 3.48$ (t, $J(HF) = 2.65$ Hz, CH_3) (A. Waterfeld, Diplomarbeit, Universität Göttingen 1977).
[11] **2a**: ^{19}F-NMR (60 MHz, SO_2, $CFCl_3$): $\delta = 54.5$ (SF); ^1H-NMR (60 MHz, SO_2, TMS): $\delta = 3.60$ ($J(F{-}CH_3) = 7.7$ Hz, CH_3), 3.48 ($J(F{-}(CH_3)_2) = 2.5$ Hz, $(CH_3)_2$) [6c]; **2b**: ^{19}F-NMR (60 MHz, SO_2, $CFCl_3$): $\delta = 54.4$ (SF); ^1H-NMR (60 MHz, SO_2, TMS): $\delta = 3.53$ ($J(F{-}CH_3) = 7.8$ Hz, CH_3), 3.44 ($J(F{-}(CH_3)_2) = 2.6$ Hz, $(CH_3)_2$).
[12] NMR data for **6**: ^{19}F-NMR (235.35 MHz, SO_2, stand. $CFCl_3$): $\delta = 76.37$ ($^2J(F{-}F) = 156.5$ Hz, SF_4), 52.43 (SF); ^1H-NMR (60 MHz, SO_2, stand. TMS): $\delta = 8.8$ (NH). The 1:1 compound $SF_5NH_2 \cdot HCl$ can be obtained at -78 °C, but at room temperature decomposes into its components: J. S. Thrasher, K. Seppelt, *Z. Anorg. Allg. Chem. 507* (1983) 7. Analogous structural and bonding behavior are expected for **6** as for the recently described isoelectronic $F_5P{-}NH_3$ (W. Storzer, D. Schomburg, G.-V. Röschenthaler, R. Schmutzler, *Chem. Ber. 116* (1983) 367). The $^2J(N{-}F_4)$ coupling observed in $F_5P{-}NH_3$ is not found in **6**.
[13] A. H. Cowley, P. E. Riley, J. S. Szobota, M. C. Walker, *J. Am. Chem. Soc. 101* (1979) 5620.
[14] General Procedure: **3**: SO_2 (5–10 mL) is condensed onto 2–3 mmol MF_5 (**a**: M = As; **b**: M = Sb) and CH_3F (slight excess); the mixture is warmed slowly to -30 °C and held at this temperature for 2–3 h until formation of $(MeOSO)^{\oplus}MF_6^{\ominus}$ is complete. The solution is then cooled again to -196 °C and **1** condensed in; the mixture is warmed slowly to room temperature and stirred for 2 d. After removal of the solvent **3a** and **3b** are isolated in quantitative yield as analytically pure solids.—**5** and **6**: 5 mL HF and MeF_5 are condensed into a cold trap (Kel–F) containing 1–2 mmol **1** or NSF_3 (molar ratio NSF_3: $AsF_5 < 1:2$) at -196 °C. After removal of the volatile products, **5** and **6** remain as almost analytically pure substances. Purer products can be obtained by dissolving the Lewis acid adducts $F_5M \cdot N{=}SF_2(NMe)_2$ or $MF_5 \cdot NSF_3$ in HF.

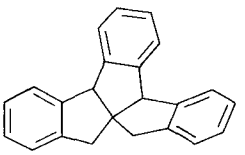
A Facile Route to Benzoannelated Centrotriquinanes

By *Dietmar Kuck**

Centropolyquinanes[1] are a fascinating group of compounds, which, as polycondensed cyclopentane hydrocarbons, have been intensively studied in recent years[2–4]. They are characterized by a central C atom shared by all cyclopentane rings. The centrohexaquinane ("C_{17}-hexaquinane") **1** represents a challenging synthetic target molecule[5].



1



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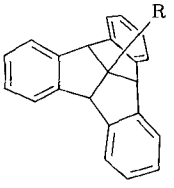

3a, R = CH_3
3b, R = $CH_2C_6H_5$
3c, R = $CH(C_6H_5)_2$

We report here a facile synthesis of benzoannelated centrotriquinanes of type **2** and **3**[6], which can be used as educts for the synthesis of higher centropolyquinanes. Key reaction in the synthesis is the double cyclodehydration of the 2,2-disubstituted 1,3-indanediols **5**, which can readily be prepared by reduction of the corresponding 1,3-indanediones **4**.

Whereas the tribenzotricyclo[6.3.0.$0^{1,5}$]undecane **2** is obtained in excellent yield[14], the 10-alkyltriben-

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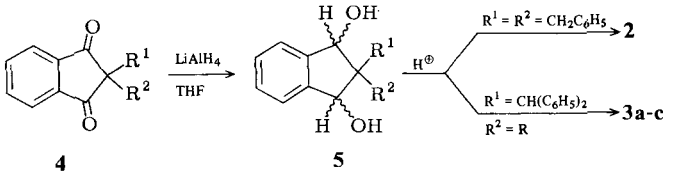

zo[5.2.1.0^{4,10}]decanes **3** have, up till now, only been accessible in moderate yields (Table 1). We attribute this to the prochirality of the benzhydryl group and, in particular, to the susceptibility of the 1,3-diol system to cleavage under acidic conditions. Moreover, the ring opening is certainly favored by the steric hindrance of the quaternary center. Of greater note therefore is the double cyclization, specifically of **5** ($R^1=R^2=CH(C_6H_5)_2$) to **3c**, whose structure, like those of other centrotriquinanes, is consistent with the spectroscopic data (Table 1)[7].

Table 1. Centrotriquinanes **2** and **3a**—**3c**. Yields, melting points, and some ^{1}H- and ^{13}C-NMR data (in parentheses) [a].

	Yield [%]	M.p. [°C]	NMR Data C(*quart*)	C(*tert*)	C(*sec*)	C_α(R)
2	92	148	(62.8)	4.44 (62.1)	3.15 [b] (44.5) 3.34 [b]	—
3a	33	239	(60.7)	4.47 (63.7)	—	1.68 (27.6)
3b	18	243	(65.2)	4.80 (61.3)	—	3.33 (45.7)
3c	26	318	(68.7)	5.10 (60.8)	—	4.60 (59.7)

[a] 80 (300) MHz, δ in $CDCl_3$. The number of signals from the aromatic groups as well as the integrated intensities and multiplicities reflect the symmetry of the compounds. [b] $^2J=-16.4$ Hz.

Under relatively mild conditions (e.g. p-$CH_3C_6H_4SO_3H$/C_6H_6) predominantly products of ring-opening form, e.g. compounds **6** and **7**[8]. However, under conditions of acid catalysis, **6** is converted into a mixture of **7** and **2**. It can therefore be assumed that the tricycles **2** and **3** are, at least in part, formed via *acyclic* intermediates of type **6**. In the UV spectra[9] of the tribenzocentrotriquinanes **3**, which have C_{3v} symmetry, the α-bands display a slight bathochromic shift relative to indane[10] ($\Delta\lambda_{max}=2.0-3.5$ nm) and have a threefold greater molar extinction in each case. In contrast, this effect is absent in **2** ($\Delta\lambda_{max}<0.5$ nm). Extensive interactions between the benzene chromophores are therefore—as in other centrotriquinanes of this type[6]—not present.

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[7] The elemental analyses and mass spectra of all compounds corroborate the compositions given.
[8] **6**: M.p. = 64—65°C (petroleum ether); ^{1}H-NMR (80 MHz, $CDCl_3$/TMS): $\delta=3.35$ (s, 2H), 3.44 (d, 1.2 Hz, 2H), 6.81 (br. s, 1H), 6.95—7.70 (m, 13H), 7.90 (m, 1H), 10.30 (s, 1H); IR (KBr): $\tilde{\nu}$ [cm^{-1}] = 2830 (w), 2730 (w), 1685 (s); MS (70 eV): m/z 312 ($M^\oplus$, 0.2%), 221 ($M^\oplus-C_7H_7$, 100), 115 ($C_9H_7^\oplus$, 28), 91 ($C_7H_7^\oplus$, 81).—**7**: M.p. = 112—113°C (C_2H_5OH); ^{1}H-NMR (80 MHz, $CDCl_3$/TMS): $\delta=2.62$, 3.17 (AB, −16.6 Hz, 4H), 3.10 (s, 2H), 5.79 (s, 1H), 6.9—7.5 (m, 13H); IR (KBr): $\tilde{\nu}=2840$ (w), 1190 (s), 1080 (s), 1070 (s), 1030 (s); MS (70 eV): m/z 312 ($M^\oplus$, 59), 221 ($M^\oplus-C_7H_7$, 67), 220 ($M^\oplus-C_7H_8$, 54), 193 (82), 179 (100), 178 (80), 91 ($C_7H_7^\oplus$, 96).
[9] UV spectra (*n*-hexane, $c=4\times10^{-4}$ to 4×10^{-5} mol L^{-1}): **2**: λ [nm] = 274.0 ($\varepsilon=4540$), 267.5 (3840), 261.0 (2310); **3a**: 276.0 (4570), 269.0 (3780), 263.5 (2350); **3b**: 276.3 (4620), 269.2 (4120), 263.0 (2850); **3c**: 276.8 (4410), 269.7 (4080), 263.5 (3010).
[10] *American Petroleum Institute (API). Research Project 44/II* (1950) 400, (1951) 414.
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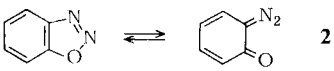
[12] R. Bloch, P. Orvane, *Synth. Commun. 11* (1981) 913.
[13] M.p. = 104—105°C (congealed oil); ^{1}H-NMR (80 MHz, $CDCl_3$/TMS): $\delta=1.30$ (d, 5.1 Hz, 2O*H*), 2.87, 2.99 (AB, −14.1 Hz, 4H), 5.18 (d, 5.1 Hz, 2H), 7.26 (m, 13H); IR (KBr): $\tilde{\nu}$ [cm^{-1}] = 3590 (m), 3430 (s).
[14] Procedure: **2**: 2,2-Dibenzyl-1,3-indanedione 4 [11] is obtained in quantitative yield from 1,3-indanedione and benzyl bromide with KF/celite 545 (Fluka) in CH_3CN, by analogy to a procedure described by *Bloch* and *Orvane* [12], and reduced with $LiAlH_4$ in tetrahydrofuran (THF) using standard methods to afford the *trans*-1,3-diol **5** ($R^1=R^2=CH_2C_6H_5$) [13] (crude yield quantitative).—A solution of this diol (3.3 g, 10 mmol) in 120 mL xylene is refluxed with 85% H_3PO_4 (1.6 g) for ca. 15 h in a water separator. The reaction solution is then washed with dilute Na_2CO_3 solution and water and dried over Na_2SO_4. After removal of the solvent an oil is formed from which **2** is obtained as fine, white needles by recrystallization from EtOH.

1,2,3-Benzoxadiazole—Detection in an Argon Matrix and in Solution**

By *Reinhard Schulz* and *Armin Schweig**

The notion that compounds such as **1** with 1,2,3-oxadiazole structures are not capable of existing[1,2] was refuted for the first time by PE spectroscopic studies on 6-diazo-2,4-cyclohexadienone **2**[3]. We report here independent experiments in a noble gas matrix and in solution which corroborate the presence of an equilibrium between 1,2,3-benzoxadiazole **1** and 6-diazo-2,4-cyclohexadienone **2**, and remove any doubts[4] surrounding our previous work[3].



If—as indicated by the results of PE spectroscopy—the diazoquinone **2** and the oxadiazole **1** both exist in the gas phase, it should be possible to freeze out both components at low temperature. The condensate formed from condensation of diazocyclohexadienone vapor **2** (vaporized at room temperature and ca. 4×10^{-2} mbar) and excess argon in a vacuum flow system at 15 K exhibits intense IR absorptions originating from a compound, which, even during recording of the spectrum, is re-converted into **2**. This retro-isomerization cannot only be followed by IR spectroscopy, but also by the naked eye due to a marked deepening of the color of the originally light yellow matrix (λ_{max} of **2** in hexane: 407 nm). The IR-induced isomerization to **2** at 15.4 K exactly follows first-order kinetics ($\tau_{1/2}=6.2$ min). By inserting a filter which transmits only

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IR radiation of long wavelength ($\lambda > 4500$ nm), the reaction could be suppressed. Only in this way could the IR spectra of the condensate in the region from 2200 to 350 cm^{-1} be recorded without simultaneous disappearance of the absorptions of the isomer.

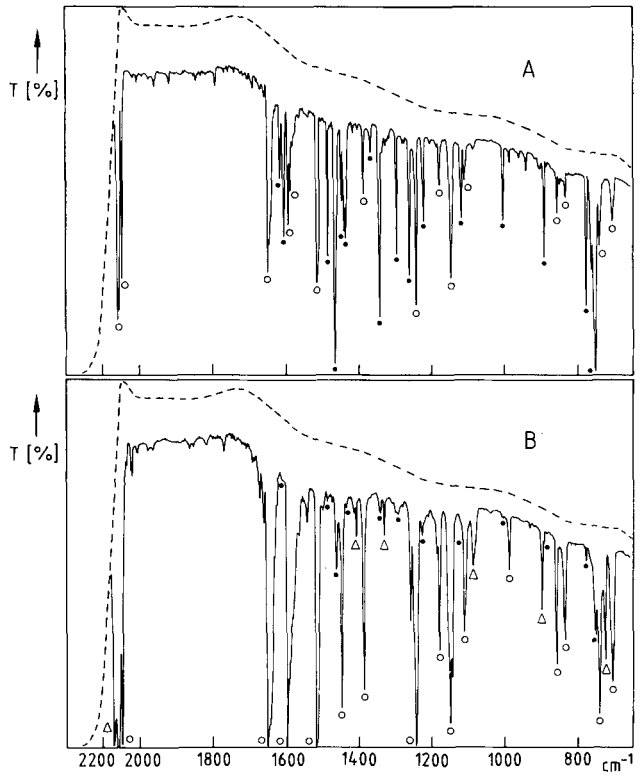
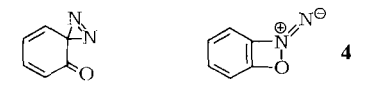


Fig. 1. IR spectra of the cocondensate of 6-diazo-2,4-cyclohexadienone **2** (20°C, $p < 0.1$ mbar) and excess argon. A: In the absence of radiation ($\lambda < 4500$ nm), B: After irradiation (60 min) by the Nernst glower of the IR spectrophotometer (Beckman IR 4250). The background caused by the IR long-pass filter is shown by the broken curves. **1**: •; **2**: ○ and **5**: △. T = transmission.

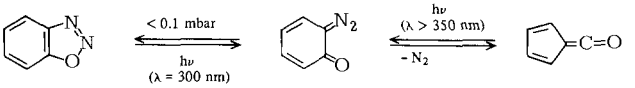
Figure 1 shows the IR spectra obtained before and after 60 minutes' irradiation with the Nernst glower of the IR spectrometer. The IR absorptions, which because of the changes in intensity are assigned to the component in equilibrium with **2**, are summarized in Table 1 and suggest a 1,2-disubstituted benzoid structure. Because of the absence of a carbonyl absorption, the diazirine **3** can certainly be ruled out. Of the remaining possible isomers of **2**, compound **4** is also precluded because of its high energy content (MNDO enthalpies of formation [kcal/mol]: **1**: 38; **2**: 49; **3**: 108, and **4**: 124). Accordingly, here—as indicated by the PE spectroscopic results in the gas phase[3]—an equilibrium between 1,2,3-benzoxadiazole **1** and the diazocyclohexadienone **2** can be assumed.

Table 1. IR absorptions of **1**, **2**, and **5** in an argon matrix.

1	1615 (m), 1605 (m), 1485 (m), 1465 (s), 1440 (m), 1437 (m), 1365 (w), 1342 (s), 1295 (m), 1261 (m), 1222 (m), 1119 (m), 1005 (m), 892 (m), 777 (m), 763 (m), 752 (s), 543 (m), 493 (m), 421 (m), 372 (m)
2	2113 (s), 2091 (m), 1650 (m), 1594 (m), 1589 (m), 1513 (m), 1446 (m), 1388 (w), 1243 (m), 1179 (w), 1147 (m), 1110 (w), 858 (w), 835 (w), 740 (m), 707 (m)
5 [7]	2138 (bs), 2080 (m), 1582 (w), 1459 (m), 1448 (m), 1407 (m), 1329 (m), 1079 (m), 899 (s), 725 (s), 634 (m), 573 (m), 518 (w)



Irradiation with light of wavelength $\lambda > 350$ nm results in selective, quantitative cleavage of the diazocyclohexadienone **2** into N_2 and 6-fulvenone **5** without decomposition of the benzoxadiazole **1**. Upon subsequent irradiation (300 nm, interference filter, width at half-height 10 nm) of the colorless matrix thus obtained, the intensities of the bands of the oxadiazole **1** decrease, and the diazocyclohexadienone **2** reappears with renewed yellow coloration of the matrix. Accordingly, **1** absorbs at ca. 300 nm and undergoes ring-opening; even the irradiation[5] of the Nernst glower ($\lambda > 2300$ nm) causes the isomerization.



1 **2** **5**

This interpretation is confirmed by UV/VIS spectroscopic studies in solution. Figure 2 shows the UV/VIS spectra of **2** in solution (A: methanol/*n*-hexane (95:5); B: *n*-hexane). Both spectra differ so markedly in the positions of the bands and their intensities that solvatochromic effects can be precluded as the reason for these differences. In contrast, the spectra are consistent with a strong solvent-dependent equilibrium between **1** and **2**, whereby

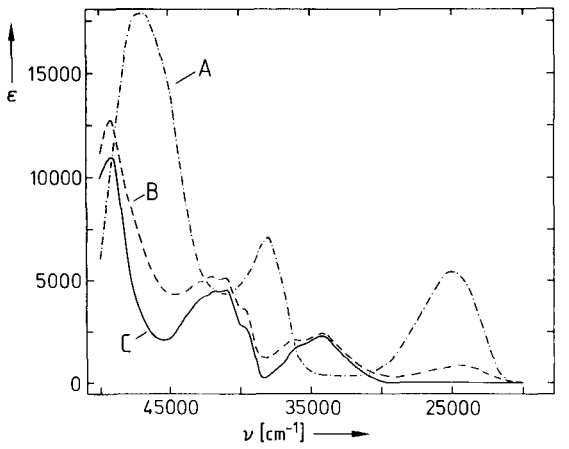


Fig. 2. UV/VIS spectra of a solution ($c = 5.83 \times 10^{-5}$ mol L^{-1}) of 6-diazo-2,4-cyclohexadienone **2** in methanol/*n*-hexane (95:5) and *n*-hexane (A and B, respectively). C: Spectrum of 1,2,3-benzoxadiazole **1** calculated from A and B.

predominantly 1,2,3-benzoxadiazole **1** occurs in apolar *n*-hexane and almost exclusively the diazoquinone **2** in methanol. From the intensity ratio of the UV/VIS bands at 400 nm, a composition of 84% **1** and 16% **2** is calculated in *n*-hexane[6]. This value is consistent with the composition determined by PE spectroscopy in the gas phase (80-90%, **1**, 10-20% **2**)[3]. The UV/VIS spectrum of **1** obtained by spectral subtraction is also shown in Figure 2 (C). Maxima occur at $\lambda = 203$, 244, and 295 nm ($\varepsilon = 11000$, 4500, and 2200, respectively) and it is very similar to the UV spectrum of 1,2,3-benzothiadiazole [λ_{max} (*n*-hexane) = 215 ($\varepsilon = 19000$), 256 (4700), and 310 nm (2300).

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[1] Review: L. A. Kazitsyna, B. S. Kikot, A. V. Upadysheva, *Russ. Chem. Rev. 35* (1966) 388.

[2] Cf. also: H. Meier, K.-P. Zeller, *Angew. Chem. 89* (1977) 876; *Angew. Chem. Int. Ed. Engl. 16* (1977) 835.

[3] R. Schulz, A. Schweig, *Angew. Chem. 91* (1979) 737; *Angew. Chem. Int. Ed. Engl. 18* (1979) 692.

[4] R. Huisgen, *Angew. Chem. 92* (1980) 979; *Angew. Chem. Int. Ed. Engl. 19* (1980) 947; there, see [91].

[5] The isomerization is a genuine photochemical process; warming the matrix from 15 K to 30 K does not influence the IR spectrum.

[6] In CCl_4 both **1** and **2** can be detected by UV (λ_{max} = 293 nm) and IR spectroscopy (ν = 1482, 1461, 1338, 1290, 1256, 1000, and 888 cm^{-1}, cf. Table 1); however, **1** cannot be detected in $CHCl_3$.

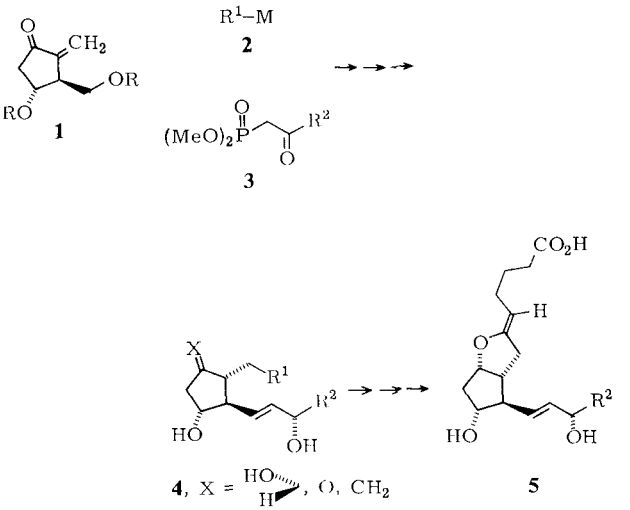
[7] Cf. also: M. Torres, A. Clement, O. P. Strausz, *J. Org. Chem. 45* (1980) 2271.

Asymmetric Synthesis of a Novel Enantiomerically Pure Prostaglandin Building Block**

By *Hans-Joachim Gais**, *Thomas Lied*, and *Karl L. Lukas*

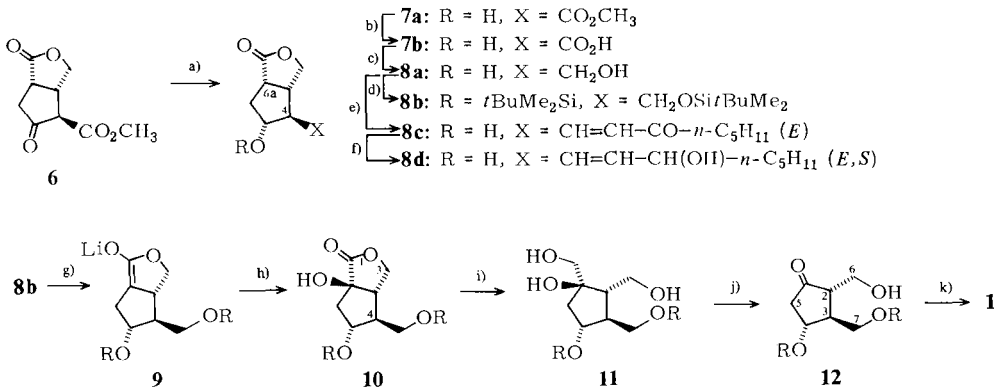
Their specific biological effects have again moved prostaglandins into the focal point of medical[1] and chemical[2] interest. 16,16-Dimethylprostaglandin E_2 **4** (X = O, R^1 = CH=CH–$(CH_2)_3$–CO_2H (*Z*), R^2 = $C(CH_3)_2$–$(CH_2)_3$–CH_3) effects cytoprotection of the gastrointestinal tract against aggressive agents[1a], while the prostacyclin **5** (R^2 = *n*-C_5H_{11}) is the most potent endogenous inhibitor of human platelet aggregation[1b].

We have developed an asymmetric synthesis of the novel, enantiomerically pure prostaglandin building block **1**, which with alkyl-, alkenyl-[3a], alkynyl-[4], and arylmetal compounds **2**[3b] as well as phosphonates **3**[2] permits attachment of various side chains R^1 and R^2 in a *1,4-addition, carbonyl-olefination strategy* and, hence, should open a general enantioselective access to prostaglandins **4** and **5**[5] (Scheme 1).



Scheme 1.

The starting material for **1** is the enantiomerically pure keto ester **6**, readily accessible by asymmetric synthesis[6]. Stereoselective reduction of **6** with $NaBH_4$ affords the hydroxy ester **7a**[6] in 91% diastereoselectivity (*ds*), in addition to 4-*epi*-**7a** (96% total yield). Recrystallization readily affords diastereomerically pure **7a** (76%); 4-*epi*-**7a** can be isomerized to **7a** using NaOMe (MeOH, 0°C). The conversion **6** → **7a** (71%) via catalytic hydrogenation is preparatively even simpler. Saponification of **7a** to the carboxylic acid **7b**[7] (92%) and its chemoselective reduction with borane-tetrahydrofuran (BH_3·THF)[8] leads to the diol **8a**[7] (78%), which is protected as the bissilyl ether **8b**[7] (91%) (Scheme 2). The decisive introduction of a hydroxy group at C-6a of **8b** to give the hydroxylactone **10**[7] (73%) is carried out by oxidation of the enolate **9**, generated by metalation of **8b** with lithium diisopropylamide (LDA), with the oxodiperoxymolybdenum-pyridine-hexamethylphosphoric



Scheme 2. [a] $NaBH_4$, MeOH, −78°C or H_2, PtO_2, ethyl acetate, 25°C, 10^5 Pa. [b] KOH, H_2O, tetrahydrofuran (THF), 0°C; 2N HCl; [c] BH_3·THF, THF, −10→25°C. [d] *t*$BuMe_2SiCl$, dimethylformamide, imidazole. [e] Me_2SO, $(COCl)_2$, NEt_3, CH_2Cl_2, −60→−20°C; $(MeO)_2P(O)$–CH(Na)–CO–*n*-C_5H_{11}, 0°C, dimethoxyethane. [f] Diisobutyl aluminum hydride/2,6-di-*tert*-butyl-4-methylphenol, toluene, −78→−40°C; 92% *ds*. [g] LDA, THF, −30°C. [h] MoOPH, −78→0°C or O_2/$P(OMe)_3$, −78→0°C. [i] $LiAlH_4$, THF, 0°C. [j] $NaIO_4$, H_2O, THF, 0°C. [k] MsCl, pyridine, −10°C; NEt_3, CH_2Cl_2, 0°C.

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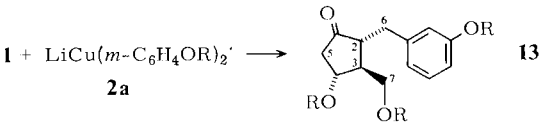
triamide complex (MoOPH)[9a] or with O_2/$P(OMe)_3$[9b]. With the reduction of **10** to the triol **11**[7] (92%), the requirements are met for the final construction of the enone structural element in the synthesis of **1**. **11** is oxidized with $NaIO_4$ to the stable hydroxy ketone **12**[7] (93%), which is then converted by $MeSO_2Cl$ (MsCl) and triethylamine into the crystalline, enantiomerically pure methylenecyclopentanone **1**[7] (89%) (Scheme 2).

A first demonstration of the synthetic potential of **1** is offered by 1,4-addition of the cuprate **2a**[3b], which affords the enantiomerically pure cyclopentanone derivative **13**[7] (88%) (Scheme 3). Comparison of the relevant ^{1}H-coupling constants of **13** ($J_{2,3}=9.0$, $J_{2,5\beta}=0.7$ Hz) with those of **12** ($J_{2,3}=10.0$, $J_{2,5\beta}=1.0$ Hz) and PGE_2 ($J_{8,12}=11.6$, $J_{8,10\beta}=1.2$ Hz) establishes the 2α-configuration. **13** is an interesting precursor for 4,5,6-trinor-3,7-*inter*-*m*-phenylene-3-oxaprostaglandins E_1 **4** (X=O, $R^2=m$-C_6H_4-OCH_2CO_2H)[3b], which are being clinically tested as selective bronchodilators for treatment of asthmatic attacks[10].



R = *t*BuMe$_2$Si

Scheme 3.

The stereoselective synthesis of **8d**[7] (total yield 70%) from **8a** via **8c**[7] demonstrates the method planned for the introduction of ω-side chains to analogous diols, which are obtained by addition of **2** to **1** via appropriate transformation of the ring-carbonyl function and removal of the protecting groups R[11] (Scheme 2).

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[7] **1**: M.p. = 18–20°C, $[\alpha]_D^{20}$ −10.1 ($c=2.75$, CH_2Cl_2), ^{1}H-NMR (300 MHz, $CDCl_3$: $\delta=2.34$ (H-5α, ddd, $J_{5\alpha,5\beta}=18.0$, $J_{4,5\alpha}=4.5$, $J_{3,5\alpha}=0.7$ Hz), 2.66 (H-5β, dd, $J_{4,5\beta}=6.0$), 2.85 (H-3, bs), 3.71 (H-7, dd, $J_{7,7}=10.0$, $J_{3,7}=5.0$), 3.76 (H-7, dd, $J_{3,7}=5.0$), 4.36 (H-4, dt, $J_{3,4}=4.0$), 5.41 (H-6-*anti*, dd, $J_{6,3}=2.5$, $J_{6,6}=1.0$), 6.12 (H-6-*syn*, dd, $J_{6,3}=2.5$).—**7b**: M.p. = 147–151°C, $[\alpha]_D^{20}$ +61.6 (2.87, MeOH).—**8a**: M.p. = 101–102°C, $[\alpha]_D^{20}$ +63.2 (1.07, MeOH).—**8b**: M.p. = 59–60°C, $[\alpha]_D^{21}$ +16.6 (0.56, ethyl acetate), ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta=2.04$ (H-4, sept., $J_{4,7}=7.0$, $J_{4,7}=6.7$, $J_{4,3a}=3.5$, $J_{4,5}=3.5$), 2.06 (H-6β, dt, $J_{6\beta,6\alpha}=13.5$, $J_{6\beta,6a}=3.0$, $J_{6\beta,5}=3.5$), 2.18 (H-6α, ddd, $J_{6\alpha,6a}=9.5$, $J_{6\alpha,5}=4.5$), 2.65 (H-3a, tt, $J_{3a,6a}=9.0$, $J_{3a,3\alpha}=9.0$, $J_{3a,3\beta}=3.5$), 2.95 (H-6a, td), 3.43 (H-7, dd, $J_{7,7}=10.0$, $J_{4,7}=7.0$), 3.50 (H-7, dd, $J_{4,7}=6.7$), 4.15 (H-5, dt), 4.24 (H-3β, dd, $J_{3\beta,3\alpha}=9.0$), 4.84 (H-3α, t).—**8c**: M.p. = 76–78°C, $[\alpha]_D^{18}$ +63.8 (0.84, ethyl acetate).—**8d**: $[\alpha]_D^{20}$ +56.1 (1.10, ethyl acetate).—**10**: M.p. = 117–119°C, $[\alpha]_D^{19}$ +28.1 (1.07, ethyl acetate), ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta=2.07$ (H-4, sept., $J_{3a,4}=3.4$, $J_{4,5}=3.2$, $J_{4,7}=7.5$, $J_{4,7}=6.5$), 2.19 (H-6β, dd, $J_{6\beta,6\alpha}=14.2$, $J_{5,6\beta}=4.9$), 2.26 (H-6α, dd, $J_{5,6\alpha}=4.0$), 2.57 (H-3a, dt, $J_{3a,3\alpha}=9.0$, $J_{3a,3\beta}=4.5$), 3.58 (H-7, m, $J_{7,7}=10.5$, $J_{4,7}=7.5$, $J_{4,7}=6.5$), 4.21 (H-3β, dd, $J_{3\alpha,3\beta}=9.0$), 4.57 (H-3α, t), 4.30 (H-5, quart.).—**11**: M.p. = 92°C, $[\alpha]_D^{18}$ −31.5 (0.22, CH_2Cl_2).—**12**: Fp = 39–40°C, $[\alpha]_D^{18}$ −82.7 (0.54, CH_2Cl_2), ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta=2.17$ (H-3, sym. m, $J_{2,3}=10.0$, $J_{3,4}=7.0$, $J_{3,7}=5.5$, $J_{3,7}=3.5$), 2.22 (H-5α, dd, $J_{5\alpha,5\beta}=18.0$, $J_{4,5\alpha}=7.5$), 2.31 (H-2, quint., $J_{2,6}=5.0$, $J_{2,6}=5.0$, $J_{2,6\beta}=1.0$), 2.68 (H-5β, ddd, $J_{4,5\beta}=7.0$), 3.32 (OH, t, $J=5.0$), 3.73 (H-7, dd, $J_{7,7}=10.0$, $J_{3,7}=5.5$), 3.81 (H-6, t), 3.86 (H-7, dd, $J_{3,7}=3.5$), 4.21 (H-4, quart.).—**13**: $[\alpha]_D^{18}$ −55.1 (0.16, *n*-hexane), ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta=1.90$ (H-3, sym. m, $J_{2,3}=9.0$, $J_{3,4}=6.6$, $J_{3,7}=3.7$, $J_{3,7}=3.0$), 2.08 (H-5α, dd, $J_{5\alpha,5\beta}=18.0$, $J_{4,5\alpha}=6.6$), 2.42 (H-2, sym. m, $J_{2,6}=7.5$, $J_{2,6}=5.2$, $J_{2,5\beta}=0.7$), 2.60 (H-5β, ddd, $J_{4,5\beta}=6.6$), 2.80 (H-6, dd, $J_{6,6}=13.5$, $J_{1,6}=7.5$), 2.93 (H-6, dd, $J_{2,6}=5.2$), 3.31 (H-7, dd, $J_{7,7}=10.5$, $J_{3,7}=3.7$), 3.65 (H-7, dd, $J_{3,7}=3.0$), 4.29 (H-4, quart.).—Selected parts of the ^{1}H-NMR spectra are reproduced. All compounds gave correct elemental analyses and were characterized by ^{1}H-NMR and IR spectra and, in part, also by ^{13}C-NMR spectra.

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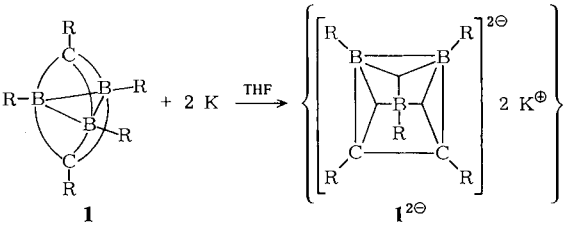
The First C_4B_6 Carbaborane**

By *Roland Köster**, *Günter Seidel*, and *Bernd Wrackmeyer*

In an investigation of the reaction of diethylborane Et_2BH with acetylene twenty years ago, we discovered a synthetic route to the first peralkylated C_2B_3 carbaborane[1] having a trigonal-pyramidal framework. Equally unexpected is our present finding that starting from pentaethyl-1,5-dicarba-*closo*-pentaborane(5) **1**[2a,b], we can prepare perethylated carbaborane **2**, which has a novel C_4B_6 skeleton.

Reaction of **1** with potassium in tetrahydrofuran (THF) at room temperature leads slowly to the formation of a dark brown solution; the metal does not react faster when the mixture is heated. If ≥0.5 mol potassium per mol **1** are taken up, two ^{11}B-NMR signals, which are shifted to high field ($\delta\approx -14$, -37; intensity ratio 2:1), appear in the ^{11}B-NMR spectrum of the weakly paramagnetic solution. The intensity of the ^{11}B-NMR signal of **1** ($\delta=+13.5$[2c]) decreases to ca. 50% after reaction of ≥1 mol potassium per mol **1**. Correspondingly, we presume that $\mathbf{1}^{2\ominus}$ is formed from a pentaethyl-*nido*-dicarbapentaborate(2$^-$) $\mathbf{1}^{2\ominus}$ (Scheme 1).



R = C_2H_5

$$2\ (\mathbf{1}^{2\ominus}K_2^{2\oplus}) + 2\ I_2 \xrightarrow[-4\ KI]{THF} (H_5C_2)_4C_4B_6(C_2H_5)_6$$
Isomers **2**

Scheme 1.

A solution of reduced **1** in THF reacts with iodine, rapidly becoming lighter in color and leading to quantitative precipitation of potassium iodide. Colorless, crystalline **2**[3] (crude yield >60%, isolated ≤25%)[4] is obtained from the yellow liquid, in addition to unreacted **1** (30–40%).

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[**] Boron Compounds, Part 60.—Part 59: R. Köster, G. Seidel, *Angew. Chem. 96* (1984) 146; *Angew. Chem. Int. Ed. Engl. 23* (1984) 155.

Comparison of the mass spectra[5] of **1** and **2** indicates that in the spectrum of **2** the peaks for the mass fragments M^+-15 and M^+-29 are practically absent; dominant are the peaks in the region of the molecular ion. At ca. 20°C, the ^{11}B-NMR spectrum of **2** consists of four signals[3]. In the ^{13}C-NMR spectrum in [D$_8$]toluene, three types of skeletal C atoms ($\delta = +37.4$, $+29.2$, and -6.3) can be observed in the ratio 1 : 2 : 1[3,6].

Compound **2** is stable to iodine and oxygen at room temperature, but in THF it is attacked by potassium to form a pale yellow solution. **2** reacts analogously to **1**[7] with anhydrous trimethylamine *N*-oxide[7] above 75°C. In refluxing toluene, 1 mol **2** liberates more than 16 mol trimethylamine from the *N*-oxide. **2** is readily soluble in aliphatic, aromatic, and many other solvents (e.g. $CHCl_3$), and can be recrystallized from diethyl ether or refluxing ethanol. On being heated from -50°C to >300°C, solid **2** undergoes endothermic and reversible phase transformations, respectively, at -21.5°C and -1.4°C (DSC[8]); because of this phase change or valence isomerization it has not yet proved possible to obtain crystals suitable for the determination of the molecular structures.

As decaethyltetracarbadecaborane(10), **2** is a valence isomer of the unknown decaethyl-2,4,6,8,9,10-hexaboraadamantane[9]; presumably the 24 valence electrons in the C_4B_6 skeleton of **2** do not, as in C_4B_6 adamantane, distribute themselves over twelve 2e2c bonds but rather over six nonlocalized 2e2c and 2e3c bonds, respectively.

2, which consists of two asymmetrically fused C_2B_3 "halves", is the first C_4B_6 carbaborane. The dimerization[10,11], which mechanistically has yet to be clarified, may be applicable to the synthesis of other organocarbaboranes with known and novel $C_xB_yH_{(x+y)}$ skeletons and of C_xH_x hydrocarbons having novel structures. The organic residues in the dimerization assume a protecting function by means of which the cluster fusion is facilitated without intermolecular condensations[12].

Compound **2** (n = 10) is an important extension to the series of carbon-rich carbaboranes $C_4B_{n-4}R_n$[10]. One possible structure for **2** is the bicapped Archimedian antiprism shown in Figure 1a; however, because of the 2n+4 skeletal electrons[13], this *closo*-type is unlikely. On the contrary, a *nido*-structure is expected for **2** (Fig. 1b). The distribution of the skeletal atoms was determined by homoscalar (^{11}B^{11}B)- and heteroscalar (^{13}C^{11}B)-correlated ^{11}B- and ^{13}C-NMR spectroscopy, respectively. By this means, using a 2D-NMR experiment (COSY[14,15]), measurable cross-peak intensities were obtained for the scalar coupling $J(^{11}B,^{11}B)$[16]. In order to explore the ^{13}C/^{11}B neighborhood, ^{11}B was selectively decoupled in the ^{13}C-NMR spectrum[17].

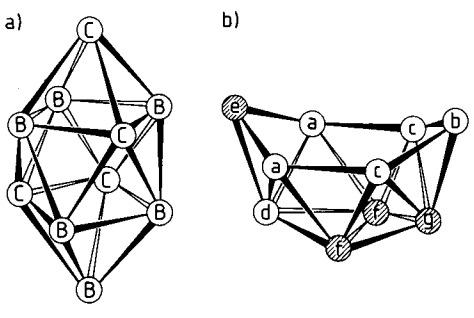

Fig. 1. a) Unlikely skeletal structure of **2**; b) Presumed skeletal structure of **2** in solution.

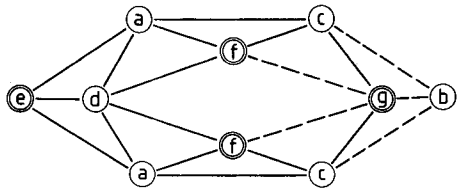

Fig. 2. Connectivities in the C_4B_6 carbaborane skeleton **2** [a].

^{11}B-Skeletal atoms $\delta(^{11}B)$		Intensity	^{13}C-Skeletal atoms $\delta(^{13}C)$		Intensity
ⓐ	−20.7	2	ⓔ	−6.3	1
ⓑ	− 6.3	1	ⓕ	29.2	2
ⓒ	6.7	2	ⓖ	37.9	1
ⓓ	50.3	1			

[a] Solid lines = detected connectivities; COSY: [14–16] ⓐ–ⓓ, ⓐ–ⓒ, ^{13}C{^{1}H, ^{11}B} [17]: ⓐ–ⓔ, ⓐ–ⓕ, ⓓ–ⓒ, ⓓ–ⓕ, ⓒ–ⓖ; broken lines = presumed connectivities.

The results of the (^{11}B^{11}B)- and (^{13}C^{11}B)-δ-correlations are shown in Figure 2. Only for boron atom ⓑ can no unequivocal connectivity be detected[18]. The number and intensities of the NMR resonances for the skeletal atoms and the linkages detected are consistent with the structure shown in Figure 1b, which is formally derived from decaborane(14) by fourfold BH_2/CEt substitution. On the basis of the present data, no statement can be made about the number and type of opened triangular faces of the polyhedron. At room temperature and above, the ^{13}C-NMR signals of the C(e,g) ethyl groups are particularly broad, which suggests a fluxional structure for the C_4B_6 skeleton.

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[2] a) R. Köster, H.-J. Horstschäfer, P. Binger, *Angew. Chem. 78* (1966) 777; *Angew. Chem. Int. Ed. Engl. 5* (1966) 730; b) R. Köster, H.-J. Horstschäfer, P. Binger, P. K. Mattschei, *Justus Liebigs Ann. Chem. 1975*, 1339; c) R. Köster, B. Wrackmeyer, *Z. Naturforsch. B 36* (1981) 704.

[3] All elemental analyses data of **2** (white crystals; subl. >270°C) are consistent with the empirical formula $C_{24}H_{50}B_6$.— ^{1}H-NMR (400 MHz, $CDCl_3$) [6]: $\delta = 1.94$ (m, 2H), 1.76 (m, 4H), 1.64 (q, 2H), 1.49 (q, 2H), 1.19 (t, 6H), 1.02 (m, 20H), 0.80 (m, broad, 14H).— ^{11}B-NMR (64.2 MHz, +28°C, $CDCl_3$): $\delta \approx 50.3$ ($W_{1/2} = 330$ Hz), 6.7 (190), −6.3 (115), −20.7 (80) in the ratio 1 : 2 : 1 : 2.- ^{13}C{^{11}B}-NMR (50.3 MHz, CD_2Cl_2) [6]: skeletal atoms: $\delta = 37.9$ (br, 1C), 29.2 (s, 2C), −6.7 (s, 1C); ethyl residues $\delta = 20.64$ (t, 1C), 20.45 (t, 2C), 20.30 (t, 1C), 16.50 (q, 1C), 14.40 (q, 2C), 12.60 (q, 1C), 11.97 (q, 2C), 11.15 (q, 1C), 10.85 (q, 2C), 10.36 (q, 1C), 9.7 (t, 1C), 6.5 (t, 2C), 4.2 (t, 3C).

[4] **1**$^{2\ominus}$: Under conditions of strict moisture- and air-exclusion, a piece of potassium (1.98 g, 50.6 mmol) is stirred for 4 d with a solution of **1** (7.82 g, 38.7 mmol) in 50 mL THF at 20°C. After pipetting off the dark brown liquid from excess potassium (bead) (0.16 g, 4.1 mmol) (consumption: 1.2 mmol K/mmol **1**), the small amount of suspended material therein is filtered off, and a weakly paramagnetic (structured ESR signal), dark THF-solution of **1**$^{2\ominus}$ is obtained [with 0.96 mmol K/mL solution (acidimetric titration)].— ^{11}B-NMR (32.1 MHz; THF): $\delta = 13.2$ (≈51%), −13.9 (≈32%), −36.4 (≈17%).— **2**: A solution of iodine (1.74 g, 6.85 mmol) in 25 mL THF is added dropwise to 14 mL of a stirred solution of **1**$^{2\ominus}$ [13.4 mmol K] in THF. The color of the solution becomes lighter and warmer ($T_{max} \approx 50$°C), and KI is precipitated. After 2 h at ca. 20°C, 2.0 g (90%) KI is filtered off and the solution concentrated in vacuo (15 mPa). The oily, solid residue is taken up in 3 mL diethyl ether, the residual KI (≈200 mg) filtered off, and **2** recrystallized by cooling the solution to −78°C. The supernatant solution is pipetted off, and the crystals are washed with cold (≤ −70°C) diethyl ether. After being dried in vacuo, 440 mg (17%) pure (GC: 99.6%) **2** is obtained. Concentration of the filtrate in vacuo (15 mPa) affords 1.8 g of a brown, viscous residue, which according to the ^{11}B-NMR spectrum, contains ca. 34% unreacted **1** and **2** (ca. 45% yield). The total yield of **2** is ca. 62%.

[5] Mass spectra: Dr. *D. Henneberg*, Max-Planck-Institut für Kohlenforschung, Mülheim a. d. Ruhr.
[6] ^{1}H- and ^{13}C-NMR data: Dr. *R. Benn*, Dr. *R. Mynott*, Max-Planck-Institut für Kohlenforschung, Mülheim a. d. Ruhr.
[7] R. Köster, Y. Morita, *Justus Liebigs Ann. Chem. 714* (1967) 70.
[8] *W. R. Scheidt*, Max-Planck-Institut für Kohlenforschung, Mülheim a. d. Ruhr.
[9] Only $H_4C_4B_6R_6$-adamantanes peralkylated at the *boron* atoms are known ($\delta(^{11}B) \approx 65$): a) $R=CH_3$: M. P. Brown, A. K. Holliday, G. M. Way, *J. Chem. Soc. Dalton Trans. 1975*, 148; b) $R=C_2H_5$: [2b].
[10] Cf. discussion of $C_nB_{12-n}H_{12}$-polyhedra ($n=2-12$) in R. N. Grimes, *Adv. Inorg. Chem. Radiochem. 26* (1983) 57f. and 114f.
[11] Cf. oxidative fusion to $R_4C_4B_8H_8$ carbaboranes: a) W. M. Maxwell, V. R. Miller, R. N. Grimes, *J. Am. Chem. Soc. 96* (1974) 7116; *Inorg. Chem. 15* (1976) 1343; b) J. R. Pipal, R. N. Grimes, *ibid. 18* (1979) 263; c) [10], p. 73–77.
[12] R. J. Wiersema, R. L. Middaugh, *J. Am. Chem. Soc. 89* (1967) 5078; R. L. Middaugh, F. Farha, Jr., *ibid. 88* (1966) 4147.
[13] M. E. O'Neill, K. Wade in R. N. Grimes: *Metal Interactions with Boron Clusters*, Plenum Press, New York 1982, p. 19–23; *Polyhedron 3* (1984) 199.
[14] A. Bax: *Two-Dimensional Nuclear Magnetic Resonance in Liquids*, Delft University Press, Dordrecht 1982; R. Benn, H. Günther, *Angew. Chem. 95* (1983) 381; *Angew. Chem. Int. Ed. Engl. 22* (1983) 390.
[15] COSY = *co*rrelated *s*pectroscop*y*: pulse sequence $(D_1\text{-}(\pi/2)\text{-}t_1\text{-}(\pi/2)\text{-}t_2)$, where D_1 (ca. 0.3 s) is the time for the system to assume thermal equilibrium, t_1, corresponding to the amount of data and the spectral width of the F_1-dimension, is incremented, and t_2 is the acquisition time corresponding to the normal 1 D-NMR spectrum. Spectra were recorded on a Bruker-WP200 instrument. The spectral width was 6000 Hz in the F_1- and F_2-axes. The data matrix consisted of 256 (t_1) × 512 (t_2) points and was filled up once in each dimension after a Lorentz-Gauss transformation in both dimensions. The cross peaks were assigned after a double Fourier transformation [16].
[16] T. L. Venable, W. C. Hutton, R. N. Grimes, *J. Am. Chem. Soc. 106* (1984) 29.
[17] A 50.3 MHz $^{13}C\{^1H$- broad band$\}$-NMR spectrum of **2** was recorded in $CDCl_3$ (ca. 5%) at 28°C. The following were compared: a) $^{13}C\{^1H,^{11}B(50.3)\}$: effect at ^{13}C (29.2), weak at $^{13}C(-6.7)$ and clear at $^{11}B(50.3)$-$^{13}CH_2$; b) $^{13}C\{^1H,^{11}B(+6.7)\}$: effect at ^{13}C (37.9), weak at ^{13}C (29.2), and clear at ^{11}B (+6.7)-$^{13}CH_2$; c) $^{13}C\{^1H,^{11}B(-6.3)\}$, effect clear only at ^{11}B (−6.3)-$^{13}CH_2$; d) $^{13}C\{^1H,^{11}B(-20.7)\}$, effect at ^{13}C (−6.7), weak at ^{13}C (29.2), and clear at ^{11}B (−20.7)-$^{13}CH_2$.
[18] This arises from relatively small scalar couplings $^1J(^{13}C^{11}B)$ and $^1J(^{11}B^{11}B)$; cf. [16].

$[Cu_6I_{11}]^{5\ominus}$—a Polyanion with Trigonal-Prismatic Arrangement of Six Metal Atoms**

By *Farbod Mahdjour-Hassan-Abadi, Hans Hartl**, and *Joachim Fuchs*

By allowing Cu to react with I_2 in the presence of organic iodides RI in polar organic solvents, we were able to prepare a series of compounds having unusual iodocuprate(I) ions[1]. Recently, with $Et_4N^{\oplus}$ as counterion, we isolated a monoclinic and a hexagonal compound of empirical formula $[Et_4N]CuI_2$[2], in addition to $[Et_4N]^1_\infty[Cu_2I_3]$[1a]. The vibrational spectra in the monoclinic phase lead one to expect the planar binuclear moiety $Cu_2I_4^{2\ominus} = [ICu(\mu\text{-}I)_2CuI]^{2\ominus}$, which was previously found in compounds with $[Ph_4P]^{\oplus}$, $[Pr_4N]^{\oplus}$, or $[Bu_4N]^{\oplus}$[3]. The hexagonal phase, from which the monoclinic phase forms upon solidification of the melt, corresponds—as indicated by the X-ray structure analysis—to the formula $[Et_4N]_6[Cu_6I_{11}]I$; in the crystal, the isolated anions $[Cu_6I_{11}]^{5\ominus}$ and $I^{\ominus}$ are therefore present in the ratio 1:1 (Fig. 1). The polyanion $[Cu_6I_{11}]^{5\ominus}$ of approximate $\frac{3}{m}2\,m$ (D_{3h}) symmetry consists

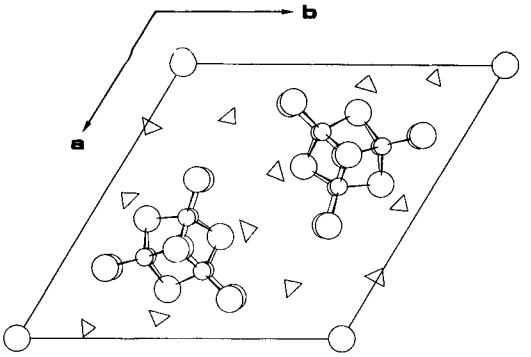

Fig. 1. Crystal structure of $[(C_2H_5)_4N]_6[Cu_6I_{11}]I$, viewing direction [001]; I: large circles, Cu: small circles, $Et_4N^{\oplus}$: triangles. Hexagonal, $P6_3/m$ (No. 176), $a = 1947.4(2)$, $b = 1212.9(3)$ pm, $Z = 2$, $\rho_{calc.} = 2.24$ g cm^{-3}; $R = 0.046$, $R_w = 0.051$ ($Mo_{K\alpha}$, Zr filter, 2723 reflections, 2153 of which with $I > 2\sigma(I)$, absorption and extinction correction, $\mu = 63.6$ cm^{-1}, anisotropic temperature factors for Cu, I, C, N; 127 refined parameters, positions of H atoms not refined). Further details of the crystal structure analysis can be obtained from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, by quoting the depository number CSD 50871, the names of the authors, and the journal citation.

of a trigonal prism of six Cu atoms; the five faces and six corners are bound to a total of eleven I atoms (Fig. 2). In this way, the Cu atoms achieve tetrahedral coordination, and the six CuI_4 tetrahedra are each condensed via three common edges to di-μ_3-iodo-tri-μ_4-iodohexakis(iodocuprate(I) $[CuI_{1/1}I_{1/3}I_{2/4}]_6^{5\ominus} = Cu_6I_{11}^{5\ominus}$.

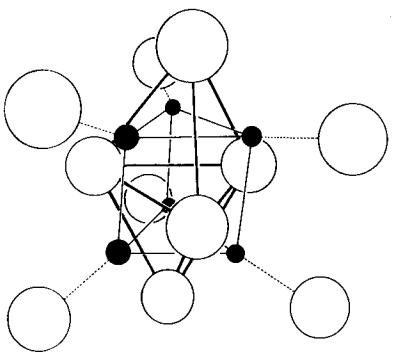

Fig. 2. Structure of the anion $[Cu_6I_{11}]^{5\ominus}$. The trigonal Cu_6-prisms and the trigonal I_5-bipyramids, respectively, are indicated by faint and bold lines. Important distances: Cu–I 256.7(3), Cu-μ_3I 270.7(2), Cu-μ_4I 273.1(2) or 274.9(2), Cu–Cu 296.1(3) (prism edge) and 341.1(3) pm (triangular side), respectively.

A trigonal-prismatic arrangement of six metal atoms without occupation of the polyhedral gaps by a further atom[4] is rare[5]; Cu_6 octahedra are the rule[6] in copper compounds. The trigonal-prismatic arrangement in $[Cu_6I_{11}]^{5\ominus}$ is not attributable to bonding Cu–Cu interactions; structure-determining is rather the close packing of the I atoms. Five I atoms form a trigonal bipyramid over whose six triangular faces six CuI_4 tetrahedra are positioned. In this way, the two tetrahedral voids in the trigonal I_5 bipyramid remain unoccupied. The Cu–Cu distances of 296.1(3) and 341.1(5) pm are considerably longer than e.g. in the anion $[Cu_5I_7]^{2\ominus}$[1c]. The additional $I^{\ominus}$ anion is separated from the anion $[Cu_6I_{11}]^{5\ominus}$ by the $Et_4N^{\oplus}$ cations.

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[**] Synthesis and Structural Investigation of Iodocuprates(I), Part 5.—Part 4: [1c].

CAS Registry numbers:
$Cu_2I_4^{\ominus}$, 75750-72-0; $[Et_4N]_6[Cu_6I_{11}]I$, 90857-65-1; $[Et_4N]Cu_2I_3$, 90839-23-9; Cu, 7440-50-8; I_2, 7553-56-2.

[1] a) H. Hartl, F. Mahdjour-Hassan-Abadi, *Angew. Chem. 93* (1981) 804; *Angew. Chem. Int. Ed. Engl. 20* (1981) 772; b) *Z. Naturforsch. B 39* (1984) 149; c) *Angew. Chem. 96* (1984) 359; *Angew. Chem. Int. Ed. Engl. 23* (1984) 378.

[2] Procedure: Tetraethylammonium iodide (2.57 g, 0.01 mol) and copper powder (2.54 g, 0.04 mol) are heated in 100 mL acetone. After addition of iodine (2.54 g, 0.01 mol), the mixture is heated until it becomes slightly yellow (N_2 stream) and is filtered hot. White needle-shaped crystals of composition $[Et_4N]Cu_2I_3$ (m.p. = 175–178 °C) precipitate out from the filtrate after a few days. Slow, dropwise addition of ether, leads to precipitation of white, needle-shaped crystals of $[Et_4N]CuI_2$-*A* (monoclinic), m.p. = 122–124 °C. Addition of benzene to the cold filtrate (ca. 5 °C) affords white, needle-shaped crystals of $[Et_4N]CuI_2$-*B* (hexagonal) (m.p. = 122–124 °C). Precipitation with benzene at room temperature gives a mixture of *A* and *B*.

[3] a) F. Mahdjour-Hassan-Abadi, H. Hartl, unpublished; b) M. Asplund, S. Jagner, M. Nilsson, *Acta Chem. Scand. A 36* (1982) 751.

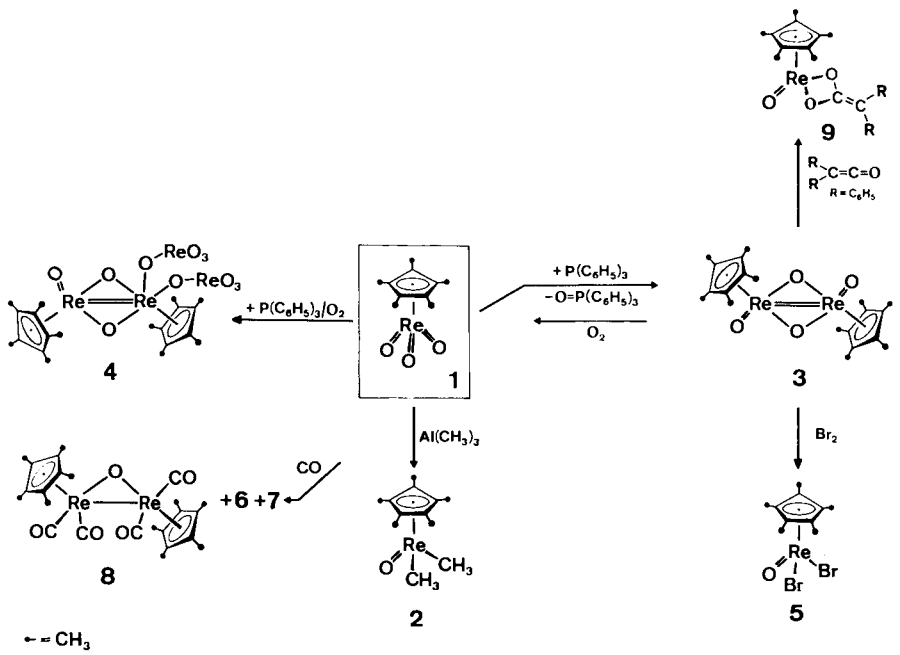
[4] Cf. e.g. V. G. Albano, M. Sansoni, P. Chini, S. Martinengo, *J. Chem. Soc. Dalton Trans. 1973*, 651.

[5] Cf. S. C. Critchlow, J. D. Corbett, *J. Am. Chem. Soc. 105* (1983) 5715.

[6] H. Dietrich, W. Storck, G. Manecke, *Makromol. Chem. 182* (1981) 2371.

route to trioxo half-sandwich complexes[1]. The d^0-Re^{VII} complex $(\eta^5\text{-}C_5Me_5)ReO_3$ **1**, surprisingly easily accessible from the isostructural tricarbonyl complex by the action of light and oxygen, can be modified in a variety of ways. We report here first examples of typical functionalization and aggregation reactions and demonstrate that both Lewis acids and Lewis bases induce partial deoxygenation processes with concomitant reduction of the metal center to yield derivatives that are very reactive.

Excess trimethylaluminum reacts instantaneously with **1** even at low temperature (−80 °C, toluene/*n*-hexane) to afford the dark red, water-stable crystalline Re^V complex **2** (> 55% isolated yield), which contains two methyl groups bonded to the metal (Scheme 1) and is sensitive to oxidation in solution[2]. Presumably an intermediate complex adduct of the oxophilic Lewis acid $Al(CH_3)_3$ is formed; subsequent transfer of methyl groups to the transition metal then leads to **2**. This reaction is general and works also with higher trialkylaluminum compounds. In contrast, the Lewis base triphenylphosphane only causes a 1:1 abstrac-



Scheme 1.

Chemistry of the Novel Oxo Half-Sandwich Complex $(\eta^5\text{-}C_5Me_5)ReO_3$: Functionalization and Aggregation**

By *Wolfgang A. Herrmann*, Ricardo Serrano, Ulrich Küsthardt, Manfred L. Ziegler, Ernst Guggolz,* and *Thomas Zahn*

In memoriam, Earl L. Muetterties

By means of exhaustive oxidative decarbonylation of metal carbonyl complexes, we have recently opened up a tion of the oxo ligands of **1**; thus, in tetrahydrofuran (THF) solution, the brown, crystalline, readily oxidizable binuclear Re^V derivative **3**, whose bridged structure is broken in air via complete reversion to the parent complex **1**, is formed slowly at room temperature; in this way, we synthesized the isotopically labeled derivatives $(\eta^5\text{-}C_5Me_5)ReO_2(*O)$ (**1**-*O; *O = ^{17}O, ^{18}O)[2]. In the presence of little atmospheric oxygen, triphenylphosphane reacts with **1** (THF, room temperature) to afford the light brown, crystalline, air-stable, diamagnetic, tetranuclear complex **4**; after recrystallization from dichloromethane/diethyl ether, the isolated yield was 40–50% (CH_2Cl_2-adduct). The surprising structure of **4** derives from that of compound **3** in that one of the terminal oxo ligands is replaced by two perrhenate groups (Fig. 1)[2].

These perrhenate groups are each bonded unsymmetrically via an oxygen atom and form an obtuse angle with the strongly distorted square-pyramidally configurated metal center Re(2). It is to be noted that the Re(1)–Re(2) distance is comparatively short (265.1(1) pm), which, al-

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[**] Multiple Bonds between Main Group Elements and Transition Metals, Part 8. This work was supported by the Deutsche Forschungsgemeinschaft, Degussa AG, and VARTA Batterie AG.—Part 7: W. A. Herrmann, R. Serrano, A. Schäfer, U. Küsthardt, M. L. Ziegler, E. Guggolz, *J. Organomet. Chem.*, in press.

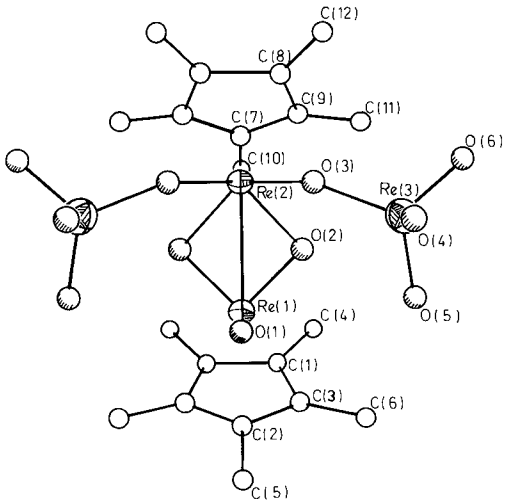

Fig. 1. Molecular structure of the tetranuclear Re^{V}/Re^{VII} complex **4** in the crystal. Rhombic, space group D_{2h}^{16}-Pcnm, $R_{iso}=0.074$, $R_w=0.036$. Important bond lengths [pm] and angles [°]: Re(1)–Re(2) 265.1(1), Re(1)–O(1) 172(1), Re(1)–O(2) 189(1), Re(2)–O(2) 199(1), Re(2)–O(3) 209.6(9), Re(3)–O(3) 177(1), Re(3)–O(4,5,6) 171(1); Re(2)–Re(1)–O(1) 95.5(5), Re(1)–Re(2)–O(3) 91.5(3), Re(1)–O(2)–Re(2) 86.2(4), Re(2)–O(3)–Re(3) 143.1(5).

though according to the noble gas formalism strongly indicates a d^2-d^2 metal-metal double bond, does not constitute strict proof of its presence[3]. In contrast, there is no doubt that the terminal oxo ligand O(1) forms a double bond with the pseudo-tetrahedrally configurated Re^{V} center[4]. The central Re_2O_2 structure is folded along the Re(1)–Re(2) vector (122°). Compound **4** has a mirror plane through the atoms Re(1), Re(2), and O(1).

The binuclear oxo complex **3** also undergoes halogenation and carbonylation reactions: elemental bromine (−80°C, CH_2Cl_2) reacts smoothly with **3** to give the green, mononuclear Re^{V} complex **5**[2]. Carbon monoxide under pressure (15 bar, THF, room temperature) effects reductive deoxygenation to afford the Re^{I} compounds (η^5-C_5Me_5)$Re(CO)_3$ **6** and (η^5-C_5Me_5)$_2Re_2(\mu$-CO)$_3$ **7**[5] in >90% total yield; in addition, traces of the novel μ-oxo complex **8**, which can be prepared better by other routes[2,6], are also produced. The structure of **8**, which has approximate C_2 symmetry, exhibits an isosceles triangular Re_2O skeleton with a Re–Re single bond of 281.7(1) pm (Fig. 2).

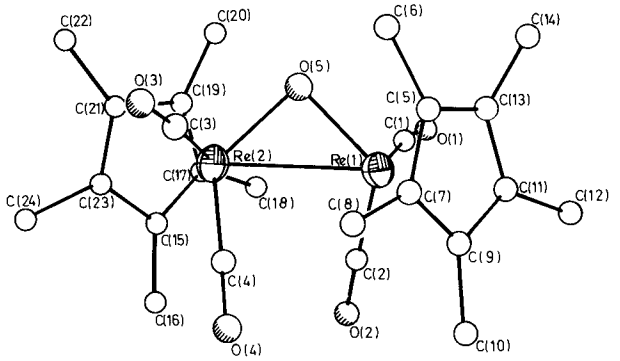

Fig. 2. Molecular structure of the (μ-oxo)carbonyl complex **8** in the crystal. Triclinic, C_i^1-$P\bar{1}$; $R_{iso}=0.068$, $R_w=0.031$. Selected bond length [pm] and angles [°]: Re(1)–Re(2) 281.7(1), Re(1)–O(5) 197.3(6), Re(2)–O(5) 197.2(8), Re–CO 186–189, C–O 115–121; Re(1)–O(5)–Re(2) 91.1(3), Re(1/2)–Re(2/1)–O(5) 44.4(2); interplanar angle between the planar C_5Me_5 ligands: 2.0°.

Further proof of the chemical lability of the bridged structure of **3** is provided by its smooth cleavage by heterocumulenes. With diphenylketene (THF, room temperature) the dark red, mononuclear complex **9** is formed quantitatively[2,7]. The dioxametallacyclobutane structure (Fig. 3) of this unprecedented compound can be attributed to a novel type of [2+2]-cycloaddition of the heterocumulene to one of the Re=O functions. The analogous reaction occurs when the trioxo complex **1** is treated with diphenylketene; here, the adduct of composition (η^5-C_5Me_5)$ReO_2[O_2CC(C_6H_5)_2]$ is formed.

Although the multiplicity of reactions undergone by the trioxo complex **1** has not yet been defined, the model reactions delineated here indicate a broad spectrum of products which should basically be realizable via deoxygenation and redox processes.

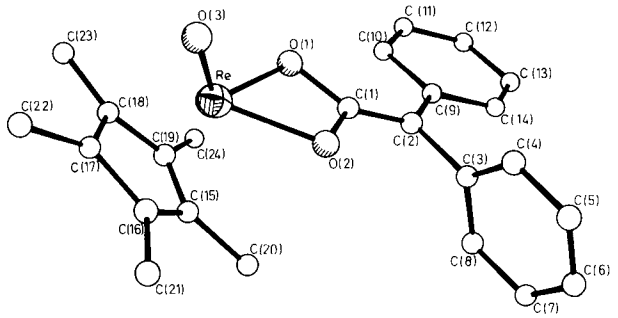

Fig. 3. Molecular structure of the dioxametallacyclobutane **9** in the crystal. Monoclinic, $P2_1/c$; $R_{aniso}=0.036$, $R_w=0.029$. Selected bond lengths [pm] and angles [°]: Re–O(3) 167.4(5), Re–O(1) 199.0(4), Re–O(2) 198.0(4), C(1)–O(1) 135.0(8), C(1)–O(2) 135.7(6), C(1)–C(2) 135.4(9); Re–O(1)–C(1) 94.7(3), Re–O(2)–C(1) 94.9(3), O(1)–Re–O(2) 65.3(1), O(1)–C(1)–O(2) 104.5(5), O(1)–C(1)–C(2) 131.9(5), O(2)–C(1)–C(2) 123.5(5), O(1)–Re–O(3) 113.3(2), O(2)–Re–O(3) 109.4(2), C(1)–Re–O(3) 118.2(2)°. The metallacycle is slightly folded along the O(1)–O(2) vector (172.7°).

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[1] W. A. Herrmann, R. Serrano, H. Bock, *Angew. Chem. 96* (1984) 364; *Angew. Chem. Int. Ed. Engl. 23* (1984) 383.

[2] **2**: Recrystallized from *n*-hexane/toluene at −78°C. IR [cm^{-1}]: ν(Re=O) = 965 vs, 955 s-vs (sh) [KBr]; 969 vs [CS_2]; ^{1}H-NMR (270 MHz, C_6D_6, 28°C): δ($C_5(CH_3)_5$) = 1.42 (s, 15H), δ($ReCH_3$) = 1.95 (s, 6H); EI-MS (70 eV): *m/z* 366 (M^+, ^{185}Re); molecular mass 372 (osmometry, C_6H_6). — In solution **3** can only be handled under conditions of strict O_2-exclusion (glove box, <1 ppm O_2). IR [cm^{-1}] (KBr): ν(ReO) = 930 s (terminal), 634 s, and 614 m (bridging); ^{1}H-NMR (270 MHz, CD_2Cl_2, 28°C): δ(CH_3) = 2.03 (s); EI-MS (70 eV): *m/z* 352 peak of highest mass ($C_5Me_5ReO_2^+$); FD-MS (toluene): *m/z* 704 (M^+, ^{185}Re). — **4**: IR [cm^{-1}] (KBr): ν(ReO) = 973 m, 934 vs (br), 899 s, 855 m (sh), 827 s (br), 729 m, 700 w, 688 w-m; ^{1}H-NMR ($CDCl_3$, 28°C): δ(CH_3 = 1.93 and 2.21 [2s, 30H], δ(CH_2Cl_2) = 5.32 (s, 2H); FD-MS (CH_2Cl_2): *m/z* 1186 (M^+, ^{185}Re); molecular mass 1180 (osmometry, $CHCl_3$). — **5**: IR [cm^{-1}] (KBr): ν(Re=O) = 965 vs, 950 sh; ^{1}H-NMR ($CDCl_3$, 28°C): δ(CH_3) = 2.28 (s); FD-MS (toluene): *m/z* 494 (M^+, ^{79}Br, ^{185}Re); molecular mass 478 (osmometry in $CHCl_3$). — **8**: IR [cm^{-1}] (KBr): ν(CO) = 1966 s, 1923 vs (br), 1865 vs (br); ^{1}H-NMR ($CDCl_3$, 28°C): δ(CH_3) = 1.98 (s); EI-MS (70 eV): *m/z* 768 (M^+, ^{185}Re). — **9**: IR [cm^{-1}] (KBr): ν(CO) = 1630 vs, 1625 vs, ν(Re=O) = 925 vs, 889 vs; ^{1}H-NMR (C_6D_6, 28°C): δ(CH_3) = 1.46 (s, 15H), δ(C_6H_5) = 7.67, 7.26, 7.03 [mc, 10H]; FD-MS (toluene): *m/z* 546 (M^+, ^{185}Re); molecular mass 550 (osmometry, C_6H_6). — Correct elemental analyses were obtained for **2**–**9**. The reagents and complexes that are air- and moisture-sensitive must be handled in an efficient glove box, particularly for the preparation of spectroscopic samples.

[3] According to the same formalism, a Re=Re double bond, as typically found in $Re_2(\mu$-$CSiMe_3)_2(CH_2SiMe_3)_4$ [*d*(Re=Re) = 255.7(1) pm], can be assumed to be present in the simpler derivative **3**: cf. M. Bochmann, G. Wilkinson, A. M. R. Galas, M. B. Hursthouse, K. M. Abdul Malik, *J. Chem. Soc. Dalton Trans. 1980*, 1797. — In principle, it also seems possi-

ble that the two oxo bridges cause the observed contraction of the Re(1)–Re(2) distance (single bond lengths normally > 280 pm); however, multiply oxygen-bridged Re complexes with considerably larger and nonbonding ReRe distances are also known (e.g., W. A. Nugent, R. L. Harlow, *J. Chem. Soc. Chem. Commun. 1979*, 1105). Cf. also the following discussions for organometallic molybdenum and tungsten complexes as well as for molybdate structures: a) M. H. Chisholm, *ACS Symp. Ser. 155* (1981) 17ff., American Chemical Society, Washington D. C. 1981; b) R. E. McCarley, T. R. Ryan, C. C. Torardi, *ibid.*, p. 41ff.; c) F. A. Cotton, D. DeMarco, L. R. Falvello, R. A. Walton, *J. Am. Chem. Soc. 104* (1982) 7375.

[4] Reference compounds: a) ReO_3Cl, d(Re=O) = 176.1(3) pm: E. Amble, S. L. Miller, A. L. Schawlaw, C. H. Townes, *J. Chem. Phys. 20* (1952) 192; b) $Re_2O_7(H_2O)_2$, d(Re=O) = 173–177 pm: H. Beyer, O. Glemser, B. Krebs, G. Wagner, *Z. Anorg. Allg. Chem. 376* (1970) 87.

[5] Proof of identity by spectral comparison (IR, MS, ^{1}H-NMR) with authentic samples, cf. J. K. Hoyano, W. A. G. Graham, *J. Chem. Soc. Chem. Commun. 1982*, 27.

[6] **8** is also formed upon short-time UV-irradiation of $(\eta^5\text{-}C_5Me_5)Re(CO)_3$ in the presence of oxygen (THF, 25°C; yields up to 30%) as well as in the reaction of **1** with $(\eta^5\text{-}C_5H_5)_2Ti(CO)_2$ (toluene, 48 h, 25°C; yield > 80%): W. A. Herrmann, R. Serrano, unpublished.

[7] Ketenes also *O*-coordinate to the oxophilic metals in titanium, vanadium, and zirconium compounds, cf. a) G. Fachinetti, C. Biran, C. Floriani, A. Chiesi-Villa, C. Guastini, *Inorg. Chem. 17* (1978) 2995; b) S. Gambarotta, M. Pasquali, C. Floriani, A. Chiesi-Villa, *ibid. 20* (1981) 1173; c) D. A. Straus, R. H. Grubbs, *J. Am. Chem. Soc. 104* (1982) 5499.—In contrast, in Mn^I complexes the ketene ligands are η^2(C,C)-coordinated, cf. d) A. D. Redhouse, W. A. Herrmann, *Angew. Chem. Int. Ed. Engl. 15* (1976) 615; e) W. A. Herrmann, J. Plank, M. L. Ziegler, K. Weidenhammer, *J. Am. Chem. Soc. 101* (1979) 3133.

A Rational Synthetic Method for 2*H*-Isoindoles**

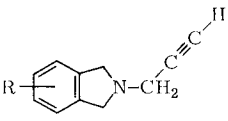
By *Richard P. Kreher** and *Norbert Kohl*

Dedicated to Professor Jan Thesing on the occasion of his 60th birthday

A straightforward synthetic concept proposed by *Thesing* et al. in 1964[1a] enabled, shortly afterwards, the first synthesis of 1*H*-isoindole **1a** and stimulated intensive studies to detect[1b] and isolate the tautomeric 2*H*-isoindole **2a**[2]. Base-induced 1,2-elimination of methanesulfinic acid from 2-mesylisoindolines is a particularly suitable method of preparing solutions containing **2a**[3]. Thermolytic methods[2] are propitious if the *o*-quinonoid hetarene is to be isolated and characterized spectroscopically; in this respect, the preparative difficulty is the time-consuming procedure of obtaining the starting materials for the thermally induced, cyclo-elimination or cycloreversion reactions. The retro-ene reaction[4] of isoindolines **3** bearing a propynyl group at the *N*-atom opens a facile route to 2*H*-isoindoles.

a, R = H; **b**, R = 5-*t*Bu, **c**, R = 4,7-Me_2

The 2-[2-propynyl]isoindolines **3** can be prepared using a simple procedure from 1,2-bis(bromomethyl)benzene, or corresponding derivatives, and 2-propynylamine by cyclizing *N*-alkylation (NEt_3, benzene, 1–8 d/room temperature)[6]. The following ^{1}H-NMR data (60 MHz, $CDCl_3$) are characteristic for **3**: δ = 3.95–4.10 (s, 4H, benzylic CH_2-groups), 3.52–3.63 (d, J = 2 Hz, 2H, propargylic CH_2-groups). Thermolysis of the isoindolines **3** (500°C/2×10^{-6} torr)[6] leads, via the—not detected—1*H*-isoindoles **1**, to the 2*H*-isoindoles **2**. In addition to ^{1}H- and ^{13}C-NMR data, the Diels-Alder reaction with *N*-(4-methylphenyl)maleimide establishes the presence of the *o*-quinonoid structure **2**. Isoindoles are also formed by cleavage of allene from **3** in the mass spectrometer.



3a, R = H(54%)
3b, R = 5-*t*Bu(57%)
3c, R = 4,7-Me_2(43%)
3d, R = 5-CO*t*Bu(68%)

According to findings on the mechanism of the retro-ene reaction[5], the intramolecular hydrogen transfer should proceed via a six-membered transition state involving an isoindoline methylene group and the CC triple bond. Activation of the CH_2-group by the benzene ring appears to be essential for the reaction. Preliminary investigations suggest that side chains having a terminal CC- or CO-double bond are less suitable for the thermolytic method, although the steric requirements for a cyclic transition state are more favorable; a non-concerted process is, therefore, not ruled out.

The facile and rational preparative method for 2*H*-isoindoles **2** combines the advantages of the thermolytic methods[2]—volatile accompanying products—with those of the base-induced elimination reaction[3]—straightforward preparation of the starting compounds—and permits the synthesis of 2*H*-isoindoles **2** with a specific substitution pattern and with anellated systems.

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[**] Studies on the Chemistry of Isoindoles and Isoindolines, Part 22. This work was supported by the Fonds der Chemischen Industrie.—Part 21: R. Kreher, K. J. Herd, *Chem.-Ztg. 106* (1982) 305.

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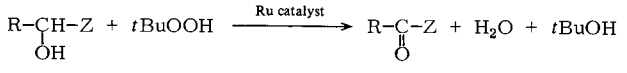
[6] **3**: A solution of 1,2-bis(bromomethyl)benzene (40–50 mmol) in 100 mL anhydrous benzene under argon at 0°C is stirred with 2-propynylamine (40—50 mmol) and triethylamine (100–125 mmol) at room temperature. After extraction with water (3 × 20 mL), the organic phase is dried with $MgSO_4$, filtered, and concentrated in vacuo; the residue is digested in 100 mL anhydrous ether and filtered. The ethereal filtrate is concentrated in vacuo and the residue dried; yields: 43–68%. The crude product **3** is distilled using a kugelrohr at 120–170°C/0.05 torr (**3a**, **b**, **d**) or fractionally recrystallized from ether (**3c**).—**2**: **3** (3 mmol) is vaporized at 45–65°C, pyrolyzed in a quartz tube (2.5 × 30 cm) at 500°C/2×10^{-6} torr, and the pyrolyzate condensed on a cold finger at −196°C. After thawing, the pyrolyzate is dissolved in 10 mL ether, *N*-(4-methylphenyl)maleimide added (2 mmol), and the mixture filtered after 24 h. The 1 : 1-adducts isolated (yield ca. 80%) are practically analytically pure.—Spectroscopic data: **2a**: ^{1}H-NMR ([D$_6$]acetone/300 MHz): δ = 6.78–6.86 (m, H-5, H-6), 7.26 (d, J = 2.9 Hz, H-1, H-3), 7.48–7.57 (m, H-4, H-7). ^{13}C-NMR ([D$_8$]dioxane/300 MHz): δ = 107.98 (d, C-1, C-3), 120.45 (d, C-4, C-7), 120.92 (d, C-5, C-6), 124.71 (s, C-3a, C-7a). 1,2,3,4-Tetrahydro-1,4-iminonaphthalene-2,3-dicarboxylic acid-*N*-(4-methylphenyl)imide: yield 82%, m.p. = 230°C (decomp.), isomer ratio: 40% *endo*- and 60% *exo*-adduct.—**2b**: ^{1}H-NMR: δ = 1.33 (s, C(CH$_3$)$_3$), 6.97–7.01 (m, H-6), 7.18–7.19 (m, H-1, H-3), 7.43–

7.48 (m, H-4, H-7). 6-*tert*-Butyl-1,2,3,4-tetrahydro-1,4-iminonaphthalene-2,3-dicarboxylic acid-*N*-(4-methylphenyl) imide: yield 83%, m.p. = 209–210°C (decomp.); isomer ratio 50:50.—**2c**: ^{1}H-NMR (60 MHz) δ = 2.38 (s, CH_3), 6.53 (s, H-5, H-6), 7.22 (d, J = 3 Hz, H-1, H-3), 10.15–11.85 (br., NH). 1,2,3,4-Tetrahydro-5,8-dimethyl-1,4-iminonaphthalene-2,3-dicarboxylic acid-*N*-(4-methylphenyl)imide: yield 75% (fractional crystallization), 30% *exo*-adduct, m.p. = 197–200°C (decomp.) and 45% *endo*-adduct, m.p. = 187–190°C.

α-Keto Esters and α-Keto Nitriles via Ruthenium-Catalyzed Dehydrogenation of α-Hydroxy Esters and Cyanohydrins with *tert*-Butyl Hydroperoxide

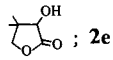
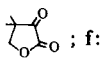
By *Masato Tanaka**, *Toshi-aki Kobayashi*, and *Toshiyasu Sakakura*

α-Keto acid derivatives are versatile intermediates in organic synthesis. Previously, we have described several methodologies for the synthesis of these compounds, including cyanation of acyl chlorides, cyanocarbonylation of organic iodides, and double carbonylation of organic halides in the presence of *sec*-amines[1–4]. We have now found that dehydrogenation of α-hydroxy esters and nitriles can be effected smoothly by *tert*-butyl hydroperoxide under very mild conditions in the presence of catalytic amounts of ruthenium compounds (Table 1).



1 **2**

a: R = Ph, Z = CO_2Et; **b**: R = 2-furyl, Z = CO_2Et;
c: R = (*E*)–PhCH=CH, Z = CO_2Et; **d**: R = CH_3, Z = CO_2CH_3;

1e:  ; **2e**:  ; **f**: R = Ph, Z = CN;

g: R = 2-thienyl, Z = CN; **h**: R = (*E*)–PhCH=CH, Z = CN

Table 1. Dehydrogenation of α-hydroxy esters and cyanohydrins with "ruthenium"-*tert*-butyl hydroperoxide systems [a].

Run	1/2	Catalyst	*T* [°C]	*t* [min]	Yield [b] [%]
1	a	$RuCl_2(PPh_3)_3$	22	60	97.5 (82.2)
2	a	$RuCl_2(PPh_3)_3$ [c]	22	60	74.2
3	a	$Ru_3(CO)_{12}$	22	60	71.0
4	a	$[RuCl_2(CO)_3]_2$	22	60	54.1
5	a	$(\eta^6\text{-}C_6H_6)RuCl_2 \cdot DMSO$	22	60	75.9
6 [d]	a	$RuCl_3$	22	60	87.5
7 [d, e]	a	$RuCl_3$	22	42	88.3
8 [d]	a	$RuBr_3$	22	12	85.0
9	a	5% Ru/C	22	60	69.9
10	a	5% Ru/C [f]	22	60	61.1
11 [d, e]	a	$Ru(acac)_3$	22	66	78.0
12 [d]	b	$RuCl_3$	22	30	(58.0)
13 [d]	c	$RuCl_3$	22	60	(64.9)
14	d	$RuCl_2(PPh_3)_3$	50	60	61.9
15	e	$RuCl_2(PPh_3)_3$	50	90	40.0
16	f	$RuCl_2(PPh_3)_3$	22	60	81.7
17 [d, e]	f	$Ru(acac)_3$	22	60	92.7 (77.0)
18 [d, e]	f	$RuBr_3$	22	100	75.6
19	g	$RuCl_2(PPh_3)_3$	22	60	84.0
20	h	$RuCl_2(PPh_3)_3$	60	300	(51.0)

[a] Reactions were run under N_2, using 5 mmol substrate, 0.05 mmol ruthenium compound, and 5 mL benzene. *tert*-Butyl hydroperoxide (70% aq. solution, 10 mmol) was added dropwise over 10 min at 22°C, and the mixture was stirred. [b] Determined by gas chromatography (isolated yields in parentheses). [c] 0.005 mmol catalyst employed. [d] In acetone. [e] In air. [f] The catalyst recovered after run 9 was reused.

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As the reactions of ethyl mandelate **1a** show (runs 1–10), the dehydrogenation is catalyzed by a variety of Ru^0, Ru^{II}, and Ru^{III} compounds; the reaction could also be effected in air as well. The Ru/C catalyst exhibited almost the same catalytic activity (No. 9) when a second reaction was run (No. 10) using recovered catalyst.

The new dehydrogenation is applicable to aromatic, heteroaromatic, and vinylic compounds; no side-products were formed. Of note is that the olefinic bond in **1c** and **1h** was not epoxidized (runs 13 and 20). This is a remarkable contrast to the well-known Sharpless oxidation, which efficiently epoxidizes allylic alcohols[5]. Fully aliphatic α-hydroxy esters, such as **1d** and **1e**, could also be dehydrogenated, albeit with somewhat low reactivity; however, α-hydroxyvaleronitrile gave only butyric acid under similar conditions.

In summary, the new procedure offers a facile synthetic route to α-keto acid derivatives from readily available starting materials.

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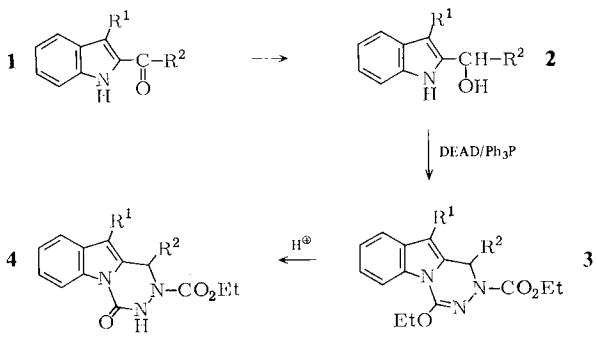
Synthesis of Substituted, Partially Hydrogenated [1,2,4]Triazino[4,5-*a*]indoles and Pyrrolo[1,2-*d*][1,2,4]triazines

By *Henning Böttcher** and *Bernd Arzt*

Dedicated to Professor Jan Thesing on the occasion of his 60th birthday

The Mitsunobu reaction, namely intermolecular dehydration with diethyl azodicarboxylate (DEAD) and triphenylphosphane, has found wide application in organic synthesis[1]. Azodicarbonyl compounds undergo cycloaddition reactions with dienes, monoenes, and 1,3-dipolar compounds[2]. We have now succeeded in preparing substituted, partially hydrogenated [1,2,4]triazino[4,5-*a*]indoles **3** and **4** by a novel cycloaddition reaction using the Mitsunobu reagent DEAD/Ph_3P. Generalization of this synthesis could lead to new interesting heterocyclic sytems.



a, $R^1 = R^2 = CH_3$; **b**, $R^1 = C_6H_5$, $R^2 = CH_3$;
c, $R^1 = CH_3$, $R^2 = CH_2\text{–}CH_2\text{–}N(CH_3)_2$,
d, $R^1 = C_6H_5$, $R^2 = CH_2\text{–}CH_2\text{–}N(CH_3)_2$

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On reduction with $NaBH_4$ in methanol (or 2-propanol) or $LiAlH_4$ in tetrahydrofuran (THF), the 2-acylindoles **1** are converted into the 2-(1-hydroxyalkyl)indole derivatives **2**. The 2-(3-dimethylaminopropionyl)indoles **1c** and **1d** are obtained from the 2-acetylindoles **1a**[3] and **1b**[4], respectively, by Mannich reaction with formaldehyde and dimethylamine. Reaction of **2** with DEAD/Ph_3P (molar ratio 1:1) in THF leads, in all cases, to crystalline products, which, according to elemental analyses, contain 1 mol of incorporated DEAD. Even addition of nucleophiles (e.g. phenol) did not lead to the substitution products to be expected in a Mitsunobu reaction. ^{1}H-NMR, IR, and mass spectroscopic data (Table 1) showed that a cycloaddition to give ethyl 1-alkyl-4-ethoxy-1,2-dihydro[1,2,4]triazino[4,5-*a*]indole-2-carboxylates **3** takes place. These can be converted by treatment with acid into the ethyl 1-alkyl-1,2,3,4-tetrahydro-4-oxo[1,2,4]triazino[4,5-*a*]indole-2-carboxylates **4**.

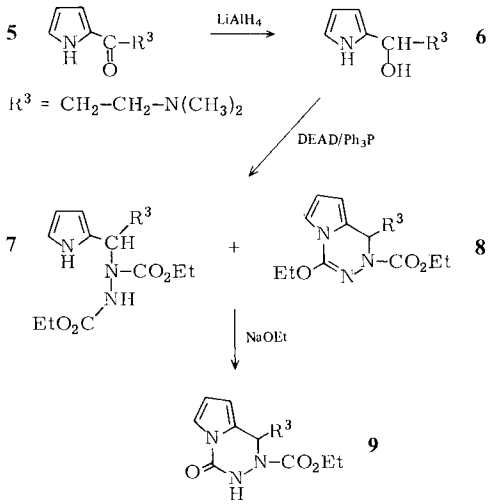

Table 1. Reaction conditions, yields, and physical and spectroscopic data of **1c**, **d**, **2a–d**, **3a**, **b**, **4a–d**, **6**, **7**, **8**, and **9**. IR [cm^{-1}], ^{1}H-NMR (δ values rel. TMS), MS (70 eV) (% rel. int.). [6].

1c: EtOH, 6h, reflux, 42%, m.p. 208–209 °C (HCl). IR (KBr): 1650 (C=O). MS: *m/z* 230 (M^+, 7), 185(6), 113(25), 58(100)

1d: EtOH, 6h, reflux, 40%, m.p. 215–216 °C (HCl) (decomp.). IR (KBr): 1650 (C=O). MS: *m/z* 292 (M^+, 9), 58(100)

2a: $NaBH_4$ in *i*PrOH/H_2O, 2h RT, yellowish oil, 99%. ^{1}H-NMR ($CDCl_3$): δ=8.5(s, 1H), 7.2–7.6 (m, 4H), 5.25 (q, 1H), 2.25 (s, 3H), 1.5 (d, 3H). MS: *m/z* 175 (M^+, 91), 160(100)

2b: $NaBH_4$ in MeOH, addition at 0 °C, 2h, 20 °C, 99%, m.p. 98–99 °C. ^{1}H-NMR ($CDCl_3$): 8.5 (s, 1H), 7.2–7.7 (m, 9H), 5.25 (q, 1H), 1.5 (d, 3H), MS: *m/z* 237 (M^+, 80), 222(100)

2c: $NaBH_4$ in MeOH, addition at 0 °C, 2h, 20 °C, 90%, m.p. 112–114 °C. ^{1}H-NMR($CDCl_3$): 8.6 (s, 1H), 7.1–7.6 (m, 4H), 5.3 (t, 1H), 3.30 (m, 2H), 2.8 (2s, 6H), 2.25 (s, 3H), 1.85–2.15 (m, 2H). MS: *m/z* 232 (M^+, 33), 58(100)

2d: $LiAlH_4$, THF, addition at 0 °C, 2h, 20 °C, 90%, m.p. 126–128 °C. ^{1}H-NMR($CDCl_3$): 8.55 (s, 1H), 7.2–7.7 (m, 9H), 5.25 (t, 1H), 3.25 (m, 2H), 2.8 (2s, 6H), 1.8–2.1 (m, 2H). MS: *m/z* 294 (M^+, 27), 58(100)

3a: THF, addition at 0 °C, 1h, 20 °C, 28%, m.p. 111–113 °C. IR (KBr): 1700 (C=O). ^{1}H-NMR ($CDCl_3$): 7.9 (m, 1H), 7.2–7.7 (2m, 3H), 5.8 (q, 1H), 4.6, 4.3 (2q, 4H), 2.25 (s, 3H), 1.6, 1.35 (2t, 6H), 1.4 (d, 3H). MS: *m/z* 315 (M^+, 65), 300(100)

3b: THF, addition at 0 °C, 1h at 20 °C, 34%, m.p. 116–117 °C. IR (KBr): 1700 (C=O). ^{1}H-NMR ($CDCl_3$): 8.0 (m, 1H), 7.2–7.7 (m, 8H), 5.85 (q, 1H), 4.6, 4.25 (2q, 4H), 1.6, 1.35 (2t, 6H), 1.4 (d, 3H). MS: *m/z* 377 (M^+, 57), 362(100)

4a: EtOH, HCl, 4h, 40 °C, 55%, m.p. 132–134 °C. IR (KBr): 1700 (C=O). ^{1}H-NMR ($CDCl_3$): 10.4 (s, 1H), 8.2 (m, 1H), 7.55 (m, 1H), 7.30 (m, 2H), 5.7 (q, 1H), 4.1 (q, 2H), 2.2 (s, 3H), 1.45 (d, 3H), 1.2 (t, 3H). MS: *m/z* 287 (M^+, 61), 200(100)

4b: Et_2O, EtOH, HCl, 2d, 20 °C, 60%, m.p. 158–160 °C. IR (KBr): 1700 (C=O). ^{1}H-NMR ($CDCl_3$): 10.7 (s, 1H), 8.25 (m, 1H), 7.2–7.7 (m, 8H), 5.65 (q, 1H), 4.1 (m, 2H), 1.5 (d, 3H), 1.15 (t, 3H). MS: *m/z* 349 (M^+, 83), 262(100)

4c: from **2c**, THF, DEAD, PPh_3, addition at 0 °C, 3h at 20 °C, 35%, m.p. 229–230 °C (HCl). IR: 1700 (C=O). ^{1}H-NMR ([D_6] DMSO): 10.5 (s, 1H), 8.0–8.2 (m, 1H), 7.2–7.7 (2m, 3H), 5.65 (t, 1H), 4.15 (q, 2H), 3.20 (t, 2H), 2.8 (2s, 6H), 2.3 (s, 3H), 2.0–2.4 (m, 2H), 1.25 (t, 3H). MS: *m/z* 344 (M^+, 10), 200(8), 58(100)

4d: from **2d**, THF, DEAD, Ph_3P, 0.5h, 20 °C, 33%, m.p. 242–243 °C (HCl) (decomp.). IR (KBr): 1700 (C=O). ^{1}H-NMR ([D_6] DMSO): 10.5 (s, 1H), 8.25 (m, 1H), 7.3–7.7 (m, 8H), 5.45 (dd, 1H), 4.12 (m, 2H), 3.05 (m, 2H), 2.75 (2s, 6H), 2.0–2.4 (m, 2H), 1.2 (t, 3H). MS: *m/z* 406 (M^+, 2), 58(100)

6: THF, $LiAlH_4$, 20 °C, 2h, 60%, m.p. 84–85 °C. ^{1}H-NMR ([D_6] DMSO): 6.6 (m, 1H), 5.9, 5.85 (2m, 2H), 4.55 (t, J=7Hz, 2H), 2.25 (m, 2H), 2.1 (2s, 6H), 1.8 (m, 2H). MS: *m/z* 168 (M^+, 17), 58(100)

7: THF, DEAD, Ph_3P, 3h, 20 °C, chromatographed with CH_2Cl_2/MeOH/AcOEt (7:2:1) as eluent, 46%, yellowish oil. IR (Film): 1700 (C=O). MS: *m/z* 238 (M^+–88, l), 167(9), 58(100)

8: as for **7**, 5%, m.p. 169–171 °C (HCl). IR (KBr): 1700 (C=O). ^{1}H-NMR ([D_6] DMSO): 7.1 (m, 1H), 6.3, 6.25 (2m, 2H), 5.6 (t, 1H), 4.35, 4.15 (2q, 4H), 2.95 (m, 2H), 2.65, 2.7 (2s, 6H), 1.95 (m, 2H), 1.25, 1.35 (2t, 6H). MS: *m/z* 308 (M^+, 5), 279(14), 136(28), 58(100)

9: NaOEt/EtOH, 6h, reflux, 20%, m.p. 199–200 °C (HCl). IR (KBr): 1700 (C=O). ^{1}H-NMR ([D_6] DMSO): 10.55 (s, 1H), 7.22 (m, 1H), 6.26, 6.19 (2m, 2H), 5.42 (t, 1H), 4.12 (q, 2H), 3.08 (t, 2H), 2.75 (2s, 6H), 1.95–2.3 (m, 2H), 1.20 (t, 3H). MS: *m/z* 207 (M^+ –73, 4), 58(100)

The scope of the reaction can be demonstrated by the reaction of DEAD/Ph_3P with dimethylamino-1-(2-pyrrolyl)-1-propanol **6**, which is obtained from the Mannich product **5**[5] by reduction with $LiAlH_4$. Under the conditions given in Table 1, **6** affords a mixture of the open-ring diethyl *N*-[3-dimethylamino-1-(2-pyrrolyl)propyl]hydrazodicarboxylate **7** and the cycloadduct **8**, which can be separated by column chromatography. **7** reacts with sodium ethoxide in ethanol with cyclization to give the ethyl 1-(2-dimethylaminoethyl)-1,2,3,4-tetrahydro-4-oxopyrrolo[1,2-*d*][1,2,4]triazine-2-carboxylate **9**.

Application of the Mitsunobu reaction to 2-(1-hydroxyalkyl)pyrrole and -indole derivatives thus leads to the cycloaddition of the DEAD reagent and opens up a facile synthetic route to novel annelated 1,2,4-triazines.

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[6] All the new compounds (Table 1) gave correct CHN analyses (within 0.3%).

Synthesis of Enantiomerically Pure 1,7-Dioxaspiro[5.5]undecanes, Pheromone Components of the Olive Fly *(Dacus oleae)***

By *Hartmut Redlich** and *Wittko Francke*

Recently, spiroacetals have awakened increasing interest as chemical communication substances[2]. Mass spectroscopic studies of this class of compounds[3] have led to the identification of 1,7-dioxaspiro[5.5]undecane as the major component in the pheromone bouquet of the female olive fly *(Dacus oleae)*[4]. However, the absolute configuration of this chiral substance of C_2 symmetry remained unknown. A few syntheses of optically active spiroacetals have been described[5], and *Schurig* et al. have succeeded in enan-

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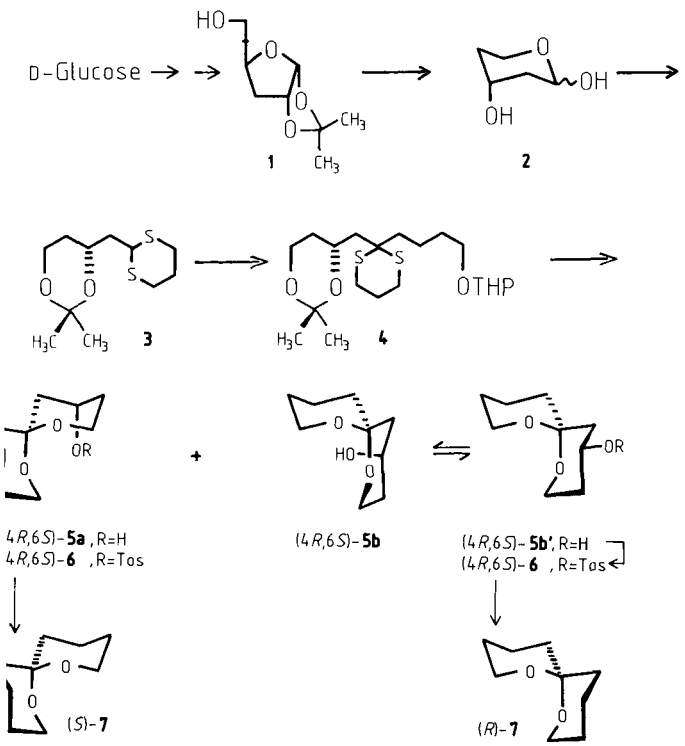
tiomeric separation of spiroacetals using complexation gas chromatography on optically-active metal complexes[6].

We have synthesized optically pure (*S*)- *and* (*R*)-1,7-dioxaspiro[5.5]undecane **7** starting from D-glucose[7]. However, since **7** possesses only one chiral center, the synthesis of the pure enantiomers using further chiral elements[1] is not possible. Instead, we used the anomeric effect, which is particularly pronounced in the 1,7-dioxaspiro[5.5]undecane system[8].

Starting material for the synthesis is the dideoxy compound **1**[5f], obtained from D-glucose. Removal of the isopropylidene group (0.5 N HCl, room temperature) by periodate cleavage (ethanol/water (1:1), $NaIO_4$ in water, 0°C) affords the free 2,4-dideoxy-D-*glycero*-pentapyranose **2**. After conversion of the latter into the open-chain dithiane (chloroform, 3 equiv. 1,3-propanedithiol, conc. HCl, 0°C), the isopropylidene compound **3** is synthesized (acetone, $CuSO_4$, catalytic amount H_2SO_4, $[\alpha]_D^{20}$ −31.5 (c=0.85 in MeOH), yield >80% for all steps). Reaction of **3** with the tetrahydropyranyl (THP) ether of 4-chlorobutanol [5g] using the Corey-Seebach method[9] [tetrahydrofuran (THF), 1.1 equiv. BuLi, −70→−20°C, 1 h, then Cl−$(CH_2)_4$−OTHP, 1 d at 0°C, 0°C→RT, 1 d, $[\alpha]_D^{20}$ −16.4 (c=1.0 in MeOH), yield 75%] affords the fully protected C_9-framework **4**.



The protecting groups in **4** can be removed in one step (acetone/water (99:1), $CuCl_2$/CuO (1:1), yield >95%). The free trihydroxy ketone cyclizes to the diastereomeric spiroacetals (4*R*,6*S*)-**5a** and (4*R*,6*R*)-**5b**/**5b**′. In (4*R*,6*S*)-**5a** the two pyran oxygen atoms are arranged in such a way that the anomeric effect is active in both pyran rings. In (4*R*,6*R*)-**5b** the anomeric effect is only active in the unsubstituted pyran ring; however, by changing its conformation to (4*R*,6*R*)-**5b**′, this molecule can also achieve an arrangement at the spirocenter in which the oxygen atoms adopt diaxial positions. Because of the equatorial position of the hydroxy group in (4*R*,6*R*)-**5b**′, this arrangement is more stable overall and this is expressed in the isomer ratio (4*R*,6*S*)-**5a**: (4*R*,6*R*)-**5b**′=3.5:6.5.

The two pure enantiomers (*S*)-**7** and (*R*)-**7** can be obtained by removal of the hydroxy group from (4*R*,6*S*)-**5a** and (4*R*,6*R*)-**5b**′, respectively. The diastereomeric hydroxy spiroacetals (4*R*,6*S*)-**5a** and (4*R*,6*R*)-**5b**′ are separated by chromatography on silica gel (ether/petroleum ether), whereby **5a**, the compound with the axial hydroxy groups, is considerably more mobile[10]. **5a** reacts slowly with tosyl chloride in pyridine to give the tosylate (4*R*,6*S*)-**6** ($[\alpha]_D^{20}$ +60.0, c=1.92 in $CDCl_3$), conversion after 3 d ca. 50%), whereas the reaction to the diastereomer (4*R*,6*R*)-**6** ($[\alpha]_D^{20}$, −56.3 (c=2.46 in $CDCl_3$) proceeds smoothly. The width of the ^{1}H-NMR signal for 4-H in (4*R*,6*S*)-**6** (400 MHz ^{1}H-NMR-spectrum, solvent $CDCl_3$, five lines at δ=4.78, overall width 14.6 Hz, corresponding to 2×a:e and 2×e:e), and in (4*R*,6*R*)-**6** (nine lines at δ=4.87, overall width 36.8 Hz, corresponding to 2×a:e and 2×a:a) confirms the assignment, which indirectly also fixes the configuration of the respective spirocenter. Elimination of the tosyl group[11] (ether, Al_2O_3, 4 h for (4*R*,6*S*)-**6**; 3—4 d for (4*R*,6*R*)-**6**) and subsequent hydrogenation (filtered ether solution, Et_3N (catalytic amount), then Pd/C/H_2, total yield >95% in each case, determined by gas chromatography) affords (*S*)-**7** and (*R*)-**7** in an optical purity of more than 95%[12]. The, to date, largest rotation value was determined for the *R*-configurated compound: $[\alpha]_D^{19}$ −122.8 (c=3.2 in pentane). Similar to 1,6-dioxaspiro[4.4]nonanes[5a], 1,7-dioxaspiro[5.5]undecane racemizes relatively easily, catalyzed by traces of acid[13].

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1, 90839-08-0; **2**, 90839-09-1; **3**, 90839-10-4; **4**, 90839-11-5; (4*R*,6*S*)-**5a**, 90898-51-4; (4*R*,6*R*)-**5b**, 90839-13-7; (4*R*,6*S*)-**6**, 90839-14-8; (4*R*,6*R*)-**6**, 90898-52-5; (*S*)-**7**, 90839-15-9; (*R*)-**7**, 90839-16-0; $HS(CH_2)_3SH$, 109-80-8; $Cl(CH_2)_4OH$, 928-51-8; (*S*)-$HO(CH_2)_2CH(OH)CH_2C(O)(CH_2)_4OH$, 90839-12-6.

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[10] (4*R*,6*S*)-**5a** ($[\alpha]_D^{21}$ +46 (c=3.0 in pentane) and (4*R*,6*R*)-**5b**′ ($[\alpha]_D^{21}$ −118° (c=3.3 in pentane) are two of the four possible isomeric 4-hydroxy-1,7-dioxaspiro[5.5]undecanes which have also been found as components of the pheromone bouquet of *Dacus aleae*. See also: R. Baker, R. Herbert, A. H. Parton, *J. Chem. Soc. Chem. Commun. 1982*, 601 and I. T. Kay, E. G. Williams, *Tetrahedron Lett. 24* (1983) 5915 (synthesis of the racemate). All four compounds can be obtained in optically pure form by inversion of the hydroxy group in (4*R*,6*S*)-**5** and (4*R*,6*R*)-**5b**, respectively. Experimental details: H. Redlich, unpublished.
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Nitrosoferrocene**

By *Max Herberhold** and *Ludwig Haumaier*

Among the ferrocene (Fc) derivatives with simple N-containing substituents[1], nitrosoferrocene has so far never been synthesized. Unsuccessful attempts to synthesize it were first described in the literature in 1959[2]. Fc-NO was postulated as a product of the electrochemical oxidation of Fc-NHOH[3], but it was neither isolated nor characterized. We have now succeeded in generating Fc-NO as a ligand in a metal complex and in isolating it for the first time after removal from the metal.

Ferrocenyllithium, Fc-Li, reacts with the η^5-cyclopentadienyl(Cp)-chromium complex $CpCr(NO)_2Cl$ under nucleophilic addition of the ferrocenyl moiety to the N atom of a nitrosyl ligand. The primary product of unknown structure can be converted into the nitrosoferrocene complex **1** using *tert*-butyl isocyanide.

$$CpCr(NO)_2Cl \xrightarrow[\text{THF}]{\text{1. Fc-Li, 2. } t\text{BuNC}} CpCr(NO)(t\text{BuNC})(\text{Fc-NO}) \quad \mathbf{1}$$

Oxidative degradation of **1** with H_2O_2 leads to liberation of nitrosoferrocene **2**. The reaction must be controlled carefully, because **2** is gradually oxidized to nitroferrocene **3** on too prolonged a treatment with H_2O_2. In contrast to **3**[4], **2** gradually decomposes at room temperature in the solid state. The violet solutions of **2** in pentane or CH_2Cl_2, on the other hand, are stable for days, even at room temperature. Starting from **2**, novel ferrocenyl compounds of the type Fc–N=X can be obtained; examples are the reactions with malonodinitrile or triethylphosphane to give **4** and **5**, respectively.

The spectroscopic data of **2**—**5** are listed in Table 1. The ^{1}H-NMR spectra show the typical pattern for ferrocenyl groups[5], and the ^{13}C-NMR spectra indicate that C-1 is much more strongly deshielded in **2** than in **3**. A similarly large difference in the chemical shift of the ring atoms C-1 (bearing the substituents) is also found in the benzene derivatives Ph–NO (δ(C-1) = 165.63) and Ph–NO_2 (δ(C-1) = 148.3)[6]. The mass spectra of **2**—**5** all show the molecular ion as a very intense peak.

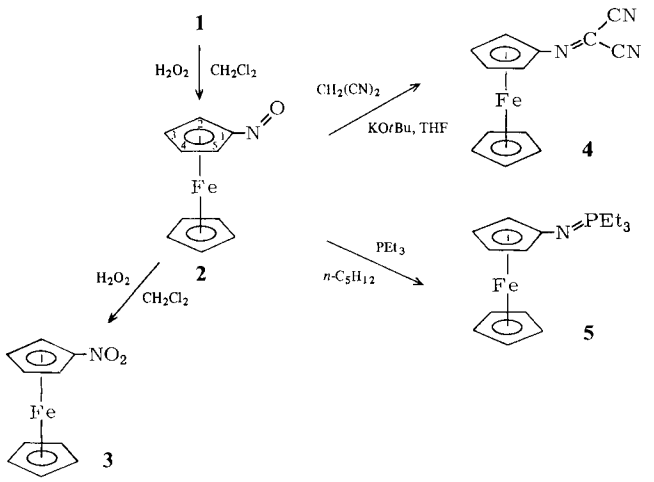

Table 1. Spectroscopic data of the compounds **2**—**5**.

	2	**3**	**4**	**5**
IR [a]:				
ν(N=X) [cm^{-1}]	1465 (X=O)		1520 (X=C(CN)$_2$)	1290 (X=PEt$_3$)
^{1}H-NMR [b]:				
$\delta(C_5H_5)$	4.27 (s)	4.31 s	4.37 s	4.05 s
δ(H-2,5)	5.27 (t)	5.23 t	5.23 t	3.81 [c]
δ(H-3,4)	4.94 t	4.49 t	5.06 t	3.78 [c], [d]
^{13}C-NMR [b]:				
$\delta(C_5H_5)$	71.4	71.6	72.6	68.5
δ(C-1)	121.1	100.6 [c]	96.8	113.1 (d, J(PC) = 2.6 Hz)
δ(C-2,5)	65.4 [c]	66.5	69.4	60.6 (d, J(PC) = 15.4 Hz)
δ(C-3,4)	74.5	70.6	75.6 [e]	62.2 [f]
MS:				
m/z (M^+)	215	231	263	317
UV/VIS [g]:				
λ_{max} (lg ε)	254 (3.80)	238 (3.96)	274 (3.82)	207 (4.45)
	294 (3.87)	272 (3.80)	349 (4.12)	273 (3.66)
	379 (3.01)	363 (3.11)	614 (3.50)	293 sh (3.60)
	523 (3.12)	468 (2.87)		453 (2.38)

[a] In CCl_4. [b] 90 MHz (^{1}H-NMR) and 22.5 MHz (^{13}C-NMR), in $CDCl_3$. [c] Broad signal. [d] $\delta(CH_3)$ = 1.15 (dt, J(HH) = 7.8 Hz, J(PH) = 16.6 Hz); $\delta(CH_2)$ = 1.85 (d, J(PH) = 12.2 Hz). [e] δ(N=C) = 100.6; δ(CN) = 112.6 and 115.2. [f] $\delta(CH_3)$ = 6.3 (J(PC) = 4.3 Hz); $\delta(CH_2)$ = 17.8 (J(PC) = 62.4 Hz). [g] In *n*-hexane.

Experimental

1: 15 mL tetrahydrofuran (THF) is added to solid Fc-Li[7] (400 mg, 2.1 mmol) at −78 °C and the mixture is treated with a solution of $CpCr(NO)_2Cl$ (425 mg, 2.0 mmol) in THF (15 mL). After warming to room temperature, 0.45 mL (4.0 mmol) *tert*-butyl isocyanide is added and the mixture heated under reflux for 15 min. The solvent is removed, the residue dissolved in CH_2Cl_2, and the resulting solution chromatographed on a 6 × 2 cm column packed with silica gel (Fluka, particle size 0.063—0.200 mm). Ferrocene and a small amount of **2** are eluted with CH_2Cl_2, while the main product **1** is washed from the column with THF. Crystallization from CH_2Cl_2/hexane gives dark violet, almost black crystals, m.p. 151 °C (decomp), yield 750 mg (84%)[8].

2: A solution of **1** (445 mg, 1.0 mmol) in CH_2Cl_2 (20 mL) is treated with 1 mL of a 10% aqueous solution of H_2O_2 and the mixture stirred vigorously. The course of the reaction is followed by thin-layer chromatography (eluent CH_2Cl_2; **1** does not elute, **2** only slowly, **3** rapidly). As soon as **1** has completely disappeared (ca. 45 min), the reaction mixture is transferred to a column (20 × 2 cm) packed with dry silica gel. A small amount of **3** is first eluted as a pale pink zone with CH_2Cl_2, followed by **2** as a blue zone. On leaving the column **2** changes color; the eluate is violet. **2** crystallizes from pentane as violet, temperature-sensitive crystals, m.p. 110 °C (decomp.), yield 140 mg (65%).

4: **2** (82 mg, 0.38 mmol) and malonodinitrile (75 mg, 1.14 mmol) are dissolved in 20 ml THF. On addition of ca. 10 mg KO*t*Bu the solution turns blue. After removal of solvent the residue is taken up in CH_2Cl_2 and the solution chromatographed on silica gel. Crystallization from pentane affords dark blue crystals of **4**, m.p. 114 °C, yield 23 mg (23%).

5: A solution of **2** (60 mg, 0.28 mmol) and triethylphosphane in pentane (20 mL) is stirred for 30 min at room temperature. The yellowish brown solution is evaporated to dryness (for removal of excess PEt_3). The residue is extracted with pentane, the extract concentrated and cooled to −20 °C. **5** crystallizes as light-brown needles, m.p. 88 °C, yield 42 mg (47%). The residue from the extraction contains a small amount of azoxyferrocene, Fc–N=N(O)–Fc, which can be purified by chromatography on silica gel (eluent CH_2Cl_2) and crystallized from CH_2Cl_2/hexane; M_r = 414 (MS).

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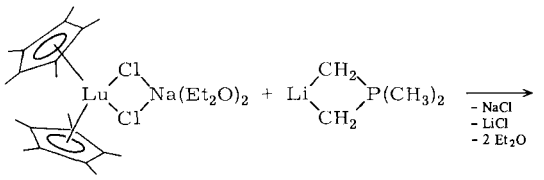
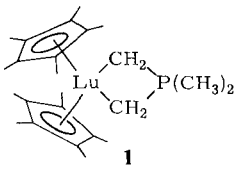
[8] Characterization of **1**: Relative molecular mass $M_r = 445$ (MS); IR [CH_2Cl_2]: ν(NC) = 2160 cm^{-1}, ν(NO) = 1645 cm^{-1}; ^{1}H-NMR (90 MHz, $CDCl_3$): $\delta = 5.32$ (s, C_5H_5Cr), 4.21 (s, C_5H_5Fe), 5.01, 4.21 (2m, C_5H_4NO), 1.47 (s, CH_3); ^{13}C-NMR (22.5 MHz, $CDCl_3$): $\delta = 99.6$ (C_5H_5Cr), 70.1 (C_5H_5Fe), 121.2, 67.4, 67.2, 63.4, 63.2 (C_5H_4NO), 30.1 (CH_3).

Pentamethylcyclopentadienyllutetium Derivatives of Dimethylphosphoniobis(methanide)**

By *Herbert Schumann*, Ilse Albrecht, Friedrich-Wilhelm Reier,* and *Ekkehardt Hahn*

Among the first organometallic compounds of the f-elements were the homoleptic ylide complexes, obtained in 1976 by reaction of the trichlorides of La, Pr, Nd, Sm, Gd, Ho, Er, and Lu with trimethylphosphoniomethanide and butyllithium. These compounds are polymeric and difficult to characterize, even in solution[2]. Use of tBu_2MePCH_2[3] or Ph_3PCH_2[4–6] allowed unequivocal spectroscopic characterization of lutetium derivatives of these ylides. Using pentamethylcyclopentadienyllutetium compounds, we have now succeeded for the first time in both synthesizing the first lutetium derivative of $[(CH_3)_2P(CH)_2]^{\ominus}$ that is configurationally stable even in solution and in performing an X-ray structure analysis of an ylide complex of the lanthanoids.





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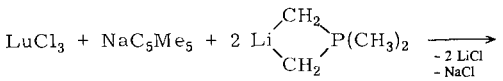

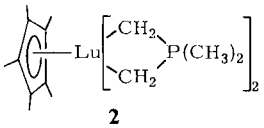

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Reaction of $(C_5Me_5)_2Lu(\mu\text{-}Cl)_2Na(Et_2O)_2$[7] with $Li[(CH_2)_2P(CH_3)_2]$ (tetrahydrofuran (THF), 25 °C, argon) affords the complex **1** in 65% yield. Complex **1**, which is extremely sensitive to air and moisture, crystallizes from pentane or ether as colorless needle-like crystals. The similarly colorless ylide complex **2** is formed analogously from $LuCl_3$, NaC_5Me_5, and $Li[(CH_2)_2P(CH_3)_2]$. The NMR spectra of **1** and **2**[8] confirm the proposed structure. Both derivatives are configurationally stable at room temperature.

The complex $Lu[(CH_2)_2P(CH_3)_2]_3$ obtained on reaction of $LuCl_3$ and $Li[(CH_2)_2P(CH_3)_2]$ in THF at 25 °C does not show a simple NMR spectrum, even at −78 °C. As in the case of $Lu[(CH_2)_2P(t\text{-}C_4H_9)_2]_3$[3], an exchange equilibrium is established between the monomeric and oligomeric association products.

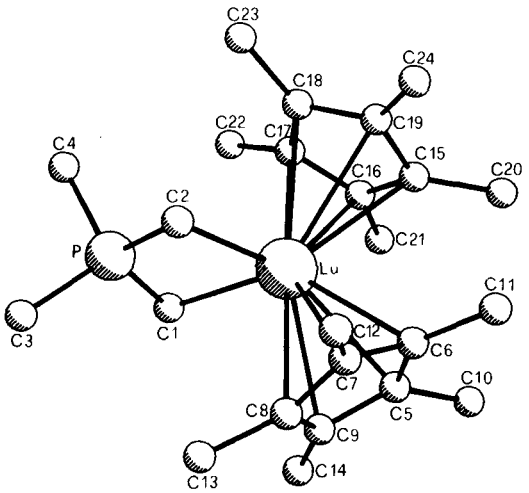

Fig. 1. Molecular structure of **1** in the crystal [9]. Selected bond lengths [Å] and angles [°]: LuCl 2.344(15), Lu-C2 2.378(15) P-C1 1.769(16), P-C2 1.782(15), P-C3 1.816(22), P-C4 1.823(23), Lu-Cp1 2.360(14), Lu-Cp2 2.493(10) (Cp1 and Cp2 are the calculated centroids of the cyclopentadienyl groups with the atoms C5 to C9 and C15 to C19), Lu-P 2.872(5); Cp1-Lu-Cp2 128.2(5), C1-Lu-C2 76.0(5), C1-P-C2 109.9(8), C1-P-C3 112.2(9), C1-P-C4 107.4(8), C2-P-C3 113.2(7), C2-P-C4 110.9(9), C3-P-C4 102.8(10).

The X-ray structure analysis shows that the Lu atom in **1** (Fig. 1 and 2)[9] is surrounded by a distorted tetrahedral array consisting of the centroids of two pentamethylcyclopentadienyl rings and two methylene carbon atoms. The Lu-C1 (2.344(15)Å) and Lu-C2 (2.378(15)Å) bond lengths lie within the range of lengths previously determined for Lu-C σ-bonds [2.376(17)Å in $(C_5H_5)_2LuCH_2Si(CH_3)_3(thf)$

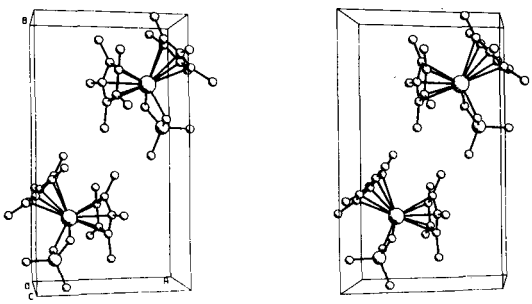

Fig. 2. Stereoview of the unit cell of **1** [9].

and 2.345(39) Å in $(C_5H_5)_2Lu$-p-C_6H_4-$CH_3(thf)$[10], yet are significantly shorter than in $[Li(dme)]_3[Lu(CH_3)_6]$ (dme = dimethoxyethane)[11], the permethylated homoleptic compound of lutetium (2.53(2) Å). The distances between the lutetium atom and the centroids of the cyclopentadienyl groups are markedly different (Lu-Cp1 2.360(14), Lu-Cp2 2.493(10) Å); however, the Lu-Cp1 distance is in good agreement with the values already known for dicyclopentadienylmetal derivatives[10]. This distortion does not occur in bis(pentamethylcyclopentadienyl) compounds of the type Cp'_2LnR_2 which have a similar structure to **1**[7]. The different Lu-Cp′ distances must therefore be interpreted in terms of electronic effects of the chelating ylide ligands and not in terms of steric interactions between the pentamethylcyclopentadienyl ligands. All the methyl groups of the C_5Me_5 ligands lie outside the planes of the C_5 rings, in each case on the side away from the lutetium (maximum deviation 0.307 Å for C13 in Cp1 and 0.437 Å for C20 in Cp2). The bond lengths P–CH_2 (1.769(16) and 1.782(15) Å) and P–CH_3 (1.816(22) and 1.823(23) Å) are in very good agreement with comparable bond lengths in ylide complexes of Ni and Co (P–CH_2 1.736(3), P–CH_3 1.825(4) and 1.795(4) Å for $[(CH_3)_2P(CH_2)_2]_4Ni_2$; P–$CH_2$ 1.734(9) and 1.717(8), P–CH_3 1.793(8) Å for $Co(CH_3)_2[P(CH_3)_3]_2[(CH_3)_2P(CH_2)_2]$[12]. The C1LuC2 angle (76.0(5)°) deviates the most from a tetrahedral angle; the phosphorus atom shows almost exact tetrahedral coordination (102.8(10)–113.2(7)°).

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[8] **1** and **2** were characterized by complete elemental analyses. M.p. and ^1H-, ^{13}C- and ^{31}P-NMR spectra (25 °C, C_6D_6, rel. TMS or H_3PO_4 ext.): **1**: m.p. 205 °C (dec); ^1H-NMR (270 MHz): $\delta = 2.11$ (s, $C_5(CH_3)_5$), 1.13 (d, $J_{PH} = 11.7$ Hz, PCH_3), −0.4 (d, $J_{PH} = 12.6$ Hz, PCH_2); ^{13}C-NMR (20.149 MHz): $\delta = 12.02$ (s, $C_5(CH_3)_5$), 114.5 (s, $C_5(CH_3)_5$), 19.1 (d, $J_{PC} = 38.8$ Hz, PCH_3), 17.8 (d, $J_{PH} = 26.4$ Hz, PCH_2); ^{31}P-NMR (32.380 MHz): $\delta = -2.2$.—**2**: m.p. 152 °C (dec.); ^1H-NMR (80 MHz): $\delta = 2.32$ (s, $C_5(CH_3)_5$), 1.17 (d, $J_{PH} = 11.7$ Hz, PCH_3), 0.06 (d, $J_{PH} = 10.8$ Hz, PCH_2); ^{13}C-NMR (20.149 MHz): $\delta = 12.04$ (s, $C_5(CH_3)_5$), 114.8 (s, $C_5(CH_3)_5$), 21.5 (d, $J_{PC} = 38.1$ Hz, PCH_3), 19.9 (d, $J_{PC} = 34.8$ Hz, PCH_2); ^{31}P-NMR (32.380 MHz): $\delta = 4.9$
[9] **1**: monoclinic, space group $P2_1$ (No. 4) $a = 9.406(14)$, $b = 15.932(26)$, $c = 8.253(11)$ Å, $\beta = 106.90(12)°$, $V = 1183.4$ Å^3, $Z = 2$, $\varrho_{calc} = 1.500$ gcm^{-3}; measurement with $Mo_{K\alpha}$ radiation at −140 °C, ω scan, for preparation of crystal see [11]. Data reduction with Lorentz and polarization corrections, no absorption correction ($\mu = 40.46$ cm^{-1}). Solution by Patterson and Fourier techniques, absolute configuration was determined, 2038 independent reflections, 1833 reflections with $I \geq 3\sigma(I)$ used for calculations. Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD 50766, the names of the authors, and the journal citation.
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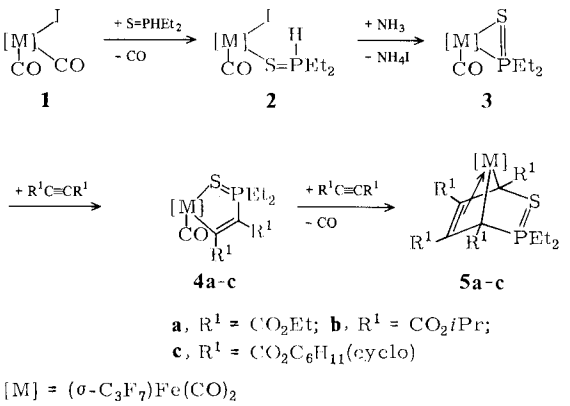
Mechanism of the Cyclocotrimerization of Diethyl(hydrido)thiophosphorus with Alkynes**

By *Ekkehard Lindner*, Claus-Peter Krieg, Wolfgang Hiller,* and *Riad Fawzi*

The cyclotrimerization of alkynes on transition metal complexes proceeds via metallacyclopropenes and -cyclopentadienes; depending on the alkyne, the products are metallacycloheptatrienes or -bicycloheptadienes[1]. Cyclocotrimerization (mixed cyclotrimerization) of alkynes and nitriles on cobalt complexes leads to pyridine derivatives[2]. The alkyne-like behavior of the P=S group (comparable atomic radii and electronegativities of P and S), which is suitable for the synthesis of otherwise difficultly accessible or even inaccessible highly substituted P- and/or S-containing heterocycles, has already been demonstrated[3].

We have now succeeded for the first time in detecting all the intermediates **2-5** participating in the cyclocotrimerization of η^2-P=S-compounds with electron-deficient alkynes. They could be characterized by elemental analyses, by their IR, ^{31}P-NMR and mass spectra (Table 1), and, in the case of **3** and **4c**, also by crystal structure investigations[4] (Fig. 1 and 2). All the intermediates contain the complex fragment $(\sigma\text{-}C_3F_7)Fe(CO)_2$.



a, $R^1 = CO_2Et$; **b**, $R^1 = CO_2iPr$;
c, $R^1 = CO_2C_6H_{11}(cyclo)$

$[M] = (\sigma\text{-}C_3F_7)Fe(CO)_2$

Table 1. Spectroscopic data and melting points of **2**, **3**, **4c**, and **5c**.

	2	**3**	**4c** [e]	**5c**
IR [cm^{-1}]	2111 w	2100 w	2110 w	—
ν(CO) [a]	2056 vs	2042 sh	2053 vs	2055 vs
	2050 sh	2036 vs	2042 s	2009 s
	554 m	531 w	538 w	545 w
ν(PS) [b]	45.2 (s)	58.7 (tt) [d]	89.1 (s)	87.5 (s)
$^{31}P\{^1H\}$-NMR [c]	558 (M^+)	430 (M^+)	708 (M^+)	959 ($M^+ + 1$)
FD-MS	34 (decomp.)	15	74	59
M.p. [°C]				

[a] In *n*-hexane. [b] In KBr. [c] In toluene, δ value, rel. 85% H_3PO_4/D_2O ext. [d] $^3J(PF) = 14.6$ Hz, $^4J(PF) = 8.2$ Hz. [e] $\nu(CC) = 1543$ cm^{-1}, m.

Reaction of the thermolabile, red-brown substitution product **2** obtainable from **1** and $SPEt_2H$ with NH_3 leads, via NH_4I-elimination, to formation of the yellow complex **3** with an η^2-bonded P=S ligand. **3**, for which there was

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previously *no* example in the series of 3d elements[5], is soluble in *n*-pentane. When $L_nM = Mn(CO)_4$[6a] and CpNi[6b] only the dimeric complexes $[L_nM(SPMe_2)]_2$ can be isolated, while the extremely unstable cleavage product $L_nM\overline{SP}Me_2$ has been trapped with alkynes. Consistent with the short-wave position of ν(PS) in the IR spectrum of **3**, the P–S distance of 201 pm (Fig. 1) reflects significant π-bonding character. The P–Fe contact is recognized by the PF couplings in the $^{31}P\{^1H\}$-NMR spectrum. The –I effect of the perfluoropropyl group in the *trans*-position to the sulfur atom stabilizes the three-membered ring **3** to such an extent that it can be isolated and identified. Oligomerization or dimerization is not observed in solution, even at 50 °C.

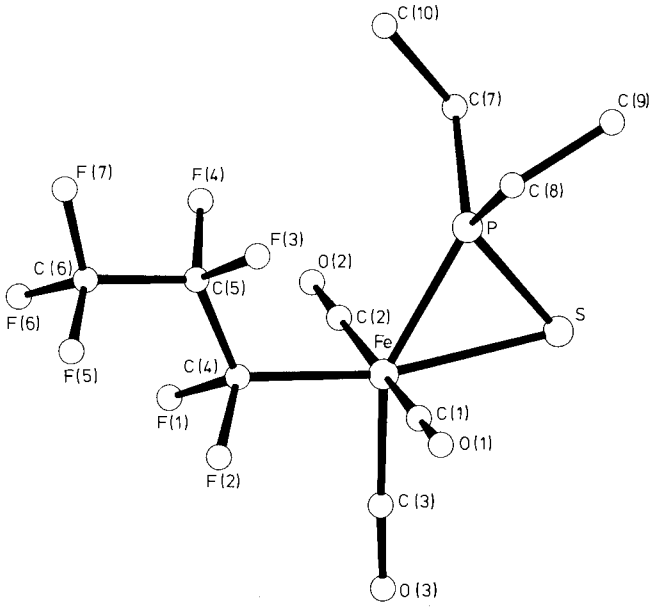

Fig. 1. Molecular structure of **3** in the crystal. Selected bond lengths [pm] and angles [°]: Fe-P 223.0(1), P-S 201.1(1), Fe-S 241.4(1), Fe-C(4) 200.1(3); P-Fe-S 51.13(3), Fe-P-S 69.16(3), Fe-S-P 59.71(3).

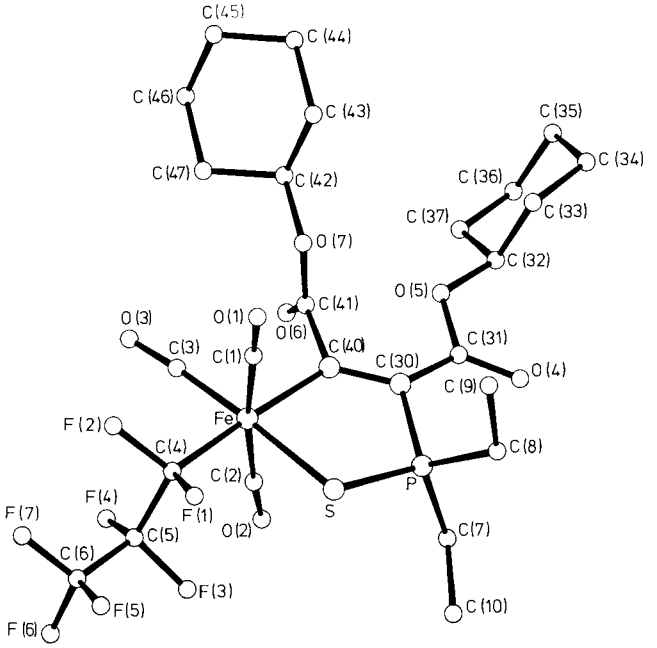

Fig. 2. Molecular structure of **4c** in the crystal. Selected bond lengths [pm] and angles [°]: Fe-S 235.6(2), S-P 200.1(3), P-C(30) 182.8(5), C(30)-C(40) 135.6(9), Fe-C(40) 200.5(7), Fe-C(4) 198.6(7); C(40)-Fe-S 87.4(2), Fe-S-P 100.9(1), S-P-C(30) 105.7(3), P-C(30)-C(40) 114.1(6), C(30)-C(40)-Fe 129.0(4).

In spite of the reduced reactivity it was demonstrated that **3** can be regarded as an intermediate of the cyclocotrimerization with electrophilic alkynes. When **3** is warmed to 50 °C in *n*-hexane, the alkyne is inserted into the Fe-P bond with formation of the bright-yellow, thermally stable ferracyclopentadienes **4a-c**. "P-Isomeric" species[5] do not occur. Typical for the almost planar metallacyclopentadiene **4c** (Fig. 2) are the short P–S and C(30)–C(40) distances, which correlate with the frequencies of ν(PS) and ν(CC) in the IR spectrum. In **4c**, the C_3F_7 group occupies the position opposite C(40).

The three CO ligands in **2-4** are always arranged meridionally, the middle CO molecule being located in the *trans*-position to the sulfur (**2, 4**) or phosphorus atom (**3**). Accordingly, the IR band which is to be assigned to this CO molecule is shifted to the long- and short-wave side, respectively, of the most intense ν_{as}(CO) band. **4a-c** react with alkynes with loss of CO to give the bright-yellow ferracycloheptadienes **5a-c**, which are only sparingly soluble in nonpolar solvents[7]. The structure follows from comparison of their analytical and spectroscopic data with those of the manganese analogues[8].

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[4] Crystallographic data: **3** crystallizes from *n*-pentane at 195 K in the monoclinic system C2/c. Lattice constants at 173 K ($Mo_{K\alpha}$ radiation): $a = 2785.8(2)$, $b = 690.7(3)$, $c = 1754.0(4)$ pm, $\beta = 107.89(37°$, $Z = 8$, $\varrho_{calc} = 1.779$ g/cm^3. Solution of structure with Multan, $R = 0.054$, (2535 reflections with $I > 3\sigma(I)$.—**4c**: triclinic, $P\bar{1}$, from *n*-hexane, lattice constants at 193 K ($Mo_{K\alpha}$ radiation): $a = 1136.7(2)$, $b = 12904(3)$, $c = 1324.0(1)$ pm, $\alpha = 110.28(2)$, $\beta = 101.94(2)$, $\gamma = 109.64(2)°$, $Z = 2$ $\varrho_{calc} = 1.473$ g/cm^3. Solution of structure with Multan, $R = 0.064$ (2750 reflections with $I > 3\sigma(I)$). Further details of the crystal structure investigations are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD 50820, the names of the authors, and the journal citation.

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[7] Typical procedure: A solution of Et_2HPS (3.0 mmol) in Et_2O (30 mL) is added dropwise at –18 °C to a solution of **1** (3.0 mmol) in Et_2O (50 mL). The stirred mixture is slowly warmed to 25 °C within 12 h. After removal of solvent and recrystallization from *n*-hexane at –30 °C, pure **2** is obtained in 70% yield. A powerful stream of NH_3 is passed through a solution of **2** (2.5 mmol) in *n*-hexane (100 mL) for 15 s, and, after removal of the solvent, two-fold extraction of the residue with 50 mL *n*-pentane, and filtration of the extracts over silica gel (5 mm), the resulting solution is evaporated down to ca. 30 mL. **3** crystallizes at –30 °C as yellow needles (yield 50%). A solution of **3** (2.5 mmol) in *n*-hexane (100 mL) and alkyne (3.0 mmol) is stirred for 6 h at 50 °C. Subsequent work-up by medium-pressure liquid chromatography with $CHCl_3$/*n*-hexane (1:5) affords **4a-c** in 15% yield and small amounts of **5a-c**. If further alkyne (3 mmol) is added to the reaction solution and stirring continued for 3 h at 60 °C, bright yellow **5a-c** are obtained after chromatographic purification (yield 20%).

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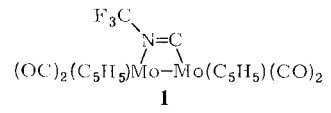
$F_3CN{=}C{=}C{=}NCF_3$, a New Bridge Ligand: Formation by CC Linkage of Two CF_3NC Ligands and Cleavage of a Mo≡Mo Bond

By *Dieter Lentz**, *Irene Brüdgam*, and *Hans Hartl*

Vibrational spectroscopic investigations have shown[1] that trifluoromethyl isocyanide CF_3NC, recently used for the first time as a complex ligand, behaves both as σ-donor and as strong π-acceptor; it thus resembles the carbonyl ligand more than other isocyanide ligands[2]. In competition with CO, CF_3NC seems to prefer the bridge position; this is demonstrated, for example, in $Fe_3(\mu\text{-}CNCF_3)(CO)_{11}$[3]. In the binuclear molybdenum complex $[Mo(\eta\text{-}C_5H_5)(CO)_3]_2$[4], the CO ligands take up exclusively the terminal positions. We have now tried to synthesize the analogous CF_3NC complex in order to check whether the CF_3NC ligand is terminally or bridge coordinated.

$$(OC)_2(C_5H_5)Mo{\equiv}Mo(C_5H_5)(CO)_2 + F_3CNC \xrightarrow[25\,^\circ C]{CH_2Cl_2}$$



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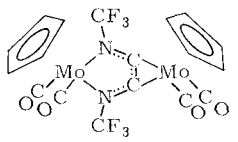
$$\mathbf{1} + n F_3CNC \xrightarrow[25\,^\circ C]{CH_2Cl_2}$$



$+ Mo_2(C_5H_5)_2(CO)_3(CNCF_3)_3$

2 **3**

Reaction of $[Mo(\eta\text{-}C_5H_5)_2(CO)_2]_2$ with CF_3NC in the molar ratio 1:1 leads to formation of $Mo_2(\eta\text{-}C_5H_5)_2(CO)_4(\eta^2\text{-}\mu\text{-}CNCF_3)$ **1**. According to the spectroscopic data[5], **1** has the same structure as the analogous phenyl isocyanide complex[6], in which the η^2-bonded isocyanide bridge ligand functions as a four-electron donor. If an excess of CF_3NC is employed, the complexes **2** and **3** are formed; these can be separated by column chromatography (silica gel, petroleum ether 40—60/CH_2Cl_2 4:1). The IR, MS, and 60 MHz ^{1}H-NMR data of **2**[5] indicated a dimeric structure analogous to that of $[Mo(\eta\text{-}C_5H_5)(CO)_3]_2$ with a molybdenum-molybdenum bond and terminal ligands. The high resolution ^{1}H- and ^{13}C-NMR spectra[5], however, showed a double set of signals for the C_5H_5-ligands, thus indicating the presence of an unsymmetrical structure. The X-ray analysis of **2**[7] gave a surprising result (Fig. 1): **2** is a complex of 1,1,1,6,6,6-hexafluoro-2,5-diaza-2,3,4-hexatriene, $F_3CN{=}C{=}C{=}NCF_3$, a molecule unknown in the free state.

Addition of a second CF_3NC molecule to **1** dimerizes the ligand via CC bond linkage and MM bond cleavage; this has hitherto rarely been observed in the Mo≡Mo system[8]. The new $F_3CN{=}C{=}C{=}NCF_3$ ligand bridges two $Mo(\eta\text{-}C_5H_5)(CO)_2$ fragments, one of which forms a five-membered MoNCCN metallaheterocycle with the bridge ligand. The second $Mo(\eta\text{-}C_5H_5)(CO)_2$ fragment is linked to the C atoms of the bridge ligand. The molybdenum, nitrogen, and carbon atoms lie in a plane (maximum deviation from the least squares plane 5 pm). The C(4)—N(1) bond length of 132.3(8) pm lies between the lengths of the CN single bonds (141.4(7) pm) and CN double bonds (127.7(7) pm) in CF_3NCHF[9]. The C(4)—C(4′) bond length of 137.6(9) pm corresponds to the length of a CC double bond. These findings indicate a strong electron delocalization in the $Mo_2(\mu\text{-}F_3CNCCNCF_3)$ system.

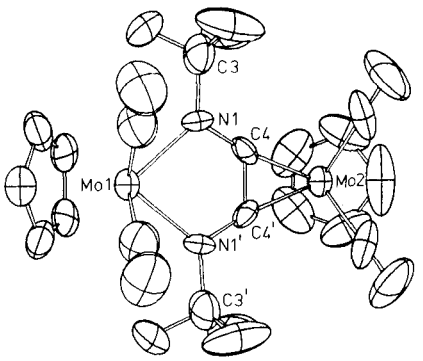


Fig. 1. Molecular structure of $[(CO)_2(\eta\text{-}C_5H_5)Mo(\mu\text{-}F_3CNCCNCF_3)Mo(\eta\text{-}C_5H_5)(CO)_2]$ **2**. Selected bond lengths: C(3)—N(1) 142(1), C(4)—N(1) 132.3(8), C(4)—C(4′) 137.6(9), Mo(1)—N(1) 223.9(6), Mo(2)—C(4) 205.6(7) pm.

The sole example known to date in which a dimeric isocyanide occurs as ligand is the complex $Cl_2(t\text{BuNC})_4Nb(\mu\text{-}t\text{BuNCCN}t\text{Bu})NbCl_4$[10]; it contains the metal atoms in different coordination spheres and oxidation states, and formation of the ligand is less easily understood than in **2**.

The composition of **3** has been determined mass spectroscopically, but insufficient reliable data are as yet available about its structure. The ^{19}F-NMR spectrum shows three signals for the three different trifluoromethyl groups, two of which couple with a small coupling constant. According to the ^{13}C-NMR spectrum, the two cyclopentadienyl groups are not equivalent.

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[2] E. Singleton, H. E. Oosthuizen, *Adv. Organomet. Chem. 22* (1983) 209.
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[4] F. C. Wilson, D. Shoemaker, *J. Chem. Phys. 27* (1957) 809.

[5] **1**: yield 30—40%, deep brown crystals, m.p. 128 °C; MS (80 eV, mass numbers referred to ^{98}Mo): *m/z* 533 (M^+), 505 (M^+-CO), 477 (M^+-2CO), 421 (M^+-4CO), and smaller fragments; IR (*n*-hexane): ν(CO) = 1993 (s), 1949 (vs), 1927 (vs), 1873 (s), ν(CN) = 1571 (br, m) cm^{-1}; ^{1}H-NMR (89.6 MHz, $CDCl_3$, TMS ext.): δ = 5.41, 5.45 (C_5H_5); ^{19}F-NMR (84.3 MHz, $CDCl_3$, $CFCl_3$ ext.): δ = −52.8 (CF_3); ^{13}C-NMR (22.5 MHz, $CDCl_3$, TMS ext.): δ = 93.6 (C_5H_5, $^1J_{CH}$ = 178 Hz), 96.0 (C_5H_5, $^1J_{CH}$ = 178 Hz), 123.6 (CF_3, $^1J_{CF}$ = 261 Hz), 226.7 (CO), 227.7 (CO), 237.2 (CN, $^3J_{CF}$ = 3.6 Hz), 243.1 (CO), 243.6 (CO).—**2**: yield 20—30%, blackish violet crystals, m.p. 210 °C (decomp.); MS (80 eV, mass numbers referred to ^{98}Mo): *m/z* 628 (M^+), 572 (M^+-2CO), and smaller fragments; IR (KBr): ν(CO) = 2008 (s), 1948 (vs), 1858 (s), ν(CN) = 1545 (m) cm^{-1}; ^{1}H-NMR (89.6 MHz, $CDCl_3$, TMS ext.): δ = 5.45, 5.46 (C_5H_5); ^{19}F-NMR (84.3 MHz, CD_2Cl_2, $CFCl_3$ ext): δ = −53.2; ^{13}C-NMR (22.5 MHz, CD_2Cl_2, TMS ext.): δ = 94.8 (C_5H_5, $^1J_{CH}$ = 181 Hz), 98.3 (C_5H_5, $^1J_{CH}$ = 179 Hz), 127.6 (CF_3, $^1J_{CF}$ = 261 Hz), 223.4 (CO), 236.3 (CN, $^3J_{CF}$ = 7.3 Hz), 263.3 (CO).—**3**: yield 5—10%, deep red-brown crystals, m.p. 87—89 °C; MS (80 eV, mass numbers referred to ^{98}Mo): *m/z* 695 (M^+), 667 ($M-CO$) and smaller fragments; IR (KBr): ν = 2019 (s), 1971 (vs), 1950 (sh), 1708 (s), 1681 (s), 1520 (s) cm^{-1}; ^{1}H-NMR (89.6 MHz, CD_2Cl_2, TMS ext.): δ = 5.81, 5.82 (C_5H_5); ^{19}F-NMR (84.3 MHz, CD_2Cl_2, $CFCl_3$ ext.): δ = −50.4 (*J* = 2 Hz), −52.8 (*J* = 2 Hz), −53.6; ^{13}C{^{1}H}-NMR (CD_2Cl_2; TMS ext.): δ = 94.7, 98.9

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(C_5H_5), 122.2 (CF_3, J_{CF} = 254 Hz), 127.0 (CF_3, J_{CF} = 261 Hz), 127.4 (CF_3, J_{CF} = 260 Hz), 221.8, 222.0, 222.3, 236.3 (m), 247.8.
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[7] Monoclinic, $P2_1/m$, a = 1083.6(3), b = 1378.6(4), c = 681.6(2) pm, β = 92.73(5)°, Z = 2; ρ_{calc} = 2.03 g cm^{-3}; R = 0.056, R_w = 0.029 ($Mo_{K\alpha}$ = 71.06 pm, 2264 reflections, 1575 with $I > 2\sigma(I)$, absorption correction (μ = 12.3 cm^{-1}), anisotropic temperature factors, no H-atom positions, 218 refined parameters). Further details of the crystal structure investigation are obtainable on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD 50861, the names of the authors, and the journal citation.
[8] a) M. D. Curtis, L. Messerle, N. A. Fotinos, R. F. Gerlach in M. H. Chisholm: *Reactivity of Metal-Metal Bonds, Am. Chem. Soc. Symp. Ser. 155* (1981) 221; b) L. K. Bell, W. A. Herrmann, M. L. Ziegler, H. Pfisterer, *Organometallics 1* (1982) 1673.
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Table 1. ESR coupling constants of the radicals $\mathbf{1}^{\odot\oplus}$–$\mathbf{3}^{\odot\oplus}$.

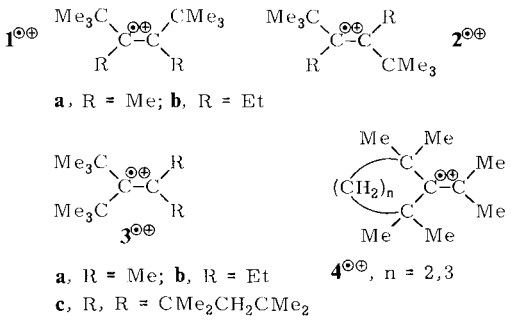
Radical	Oxidation method [a]	T [°C]	$a^{H}_{CMe_3}$ [G]	a^{H}_{R} [G]
$\mathbf{1a}^{\odot\oplus}$	A	− 85	1.7 (6H)	14.2 (6H)
$\mathbf{1b}^{\odot\oplus}$	B	− 90	1.6 (6H)	23.0 (2H) 1.6 (2H)
$\mathbf{2a}^{\odot\oplus}$	B	− 110 to − 40	0.65 (18H) [b]	14.8 (6H) [b]
$\mathbf{2b}^{\odot\oplus}$	B	− 61	0.65 (18H)	15.9 (2H) [c] 9.3 (2H) [c]
$\mathbf{3a}^{\odot\oplus}$	A, B,	− 90	2.5 (6H)	12.5 (6H)
	B	− 45	0.87 (18H)	12.5 (6H)
$\mathbf{3b}^{\odot\oplus}$	B	− 110	2.5 (6H)	13.2 (2H) [c] 9.5 (2H) [c]
$\mathbf{3c}^{\odot\oplus}$	A	− 88	2.9 (6H)	—

[a] A: electrochemically, B: with $AlCl_3$. [b] In [10], these data have been erroneously assigned to $\mathbf{3}^{\odot\oplus}$. In the meantime we have found that **3a** isomerizes to **2a** in the presence of $AlCl_3$. [c] Line-broadening effects by hindered rotation of the ethyl groups.

Hindered Rotation of *tert*-Butyl Groups in Radical Cations of Highly Substituted Alkenes**

By *Horst Eierdanz, Siegfried Potthoff, Rudolf Bolze,* and *Armin Berndt**

Hindered rotation of *tert*-butyl groups bound to sp^2 C-atoms has hitherto only been observed in 1,8-di-*tert*-butylnaphthalenes[1] and has been predicted for *Z*-1,2-di-*tert*-butylethene **1** (R = H) on the basis of force field calculations[2,3]. Herein we describe with the radical cations $\mathbf{1}^{\odot\oplus}$ and $\mathbf{3}^{\odot\oplus}$ the first examples of hindered rotation of sp^2 C-bonded *Z*-vicinal and geminal *tert*-butyl groups.



The radicals $\mathbf{1}^{\odot\oplus}$-$\mathbf{3}^{\odot\oplus}$ were generated by electrochemical oxidation of the corresponding alkenes[7] on a gold spiral as anode (platinum wire as counter electrode) or by oxidation with $AlCl_3$ in dichloromethane at −80 to −100°C. The ESR coupling constants are collected in Table 1.

In the radicals $\mathbf{1}^{\odot\oplus}$ and $\mathbf{3}^{\odot\oplus}$ only six of the eighteen *tert*-butyl protons lead to a splitting in the ESR spectrum at low temperatures. Only $\mathbf{3a}^{\odot\oplus}$ is stable enough to be investigated in the temperature range of the intermediate and fast exchange of the six with the remaining twelve γ protons. The analysis of the ESR spectra of $\mathbf{3a}^{\odot\oplus}$ (Fig. 1) gives a rotation barrier of E_A = 4.7 kcal/mol[11]. By replacing one of the six methyl groups of the *tert*-butyl groups in $\mathbf{3}^{\odot\oplus}$ by a trideuteriomethyl group we were able to prove that the phenomenon under investigation involves a hindered rotation of the *tert-butyl groups* and *not of the methyl groups* as in the neopentyl radical[12]. The ESR spectrum of the deuterated radical shows a splitting at −90° by six *tert*-butyl protons, while in the case of hindered rotation of the methyl groups a splitting by only five *tert*-butyl protons is to be expected[13].

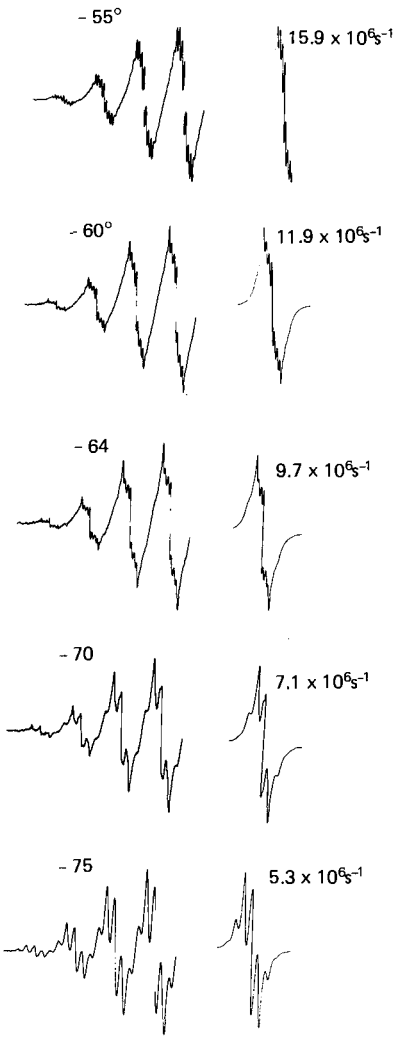


Fig. 1. Downfield halves of the ESR spectra of $\mathbf{3a}^{\odot\oplus}$ at various temperatures (left) and simulations of the central multiplet with the pertinent rate constants of the exchange (right).

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The hindered rotation of the *tert*-butyl groups in $3^{\odot\oplus}$ is consistent with the relatively high barriers of ring inversion which we have recently demonstrated for the radicals $4^{\odot\oplus}$[10, 14].

The free rotation down to -110°C of the *tert*-butyl groups of the radicals $2^{\odot\oplus}$ of *E*-1,2-di-*tert*-butylalkenes, isomeric to $1^{\odot\oplus}$, shows that hindered rotation of sp^2 C-bonded *tert*-butyl groups occurs only when two *tert*-butyl groups are in close neighborhood (1,1-, *Z*-1,2-, or "*endo*"-1,3-position in $3^{\odot\oplus}$, $1^{\odot\oplus}$, and 1,8-di-*tert*-butylnaphthalenes). This finding is consistent with the assumption of a correlated rotation[2] of the two *tert*-butyl groups.

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[3] Hindered rotation of other sp^2 C-bonded alkyl groups, e.g. in alkenes or their radical cations: $(CH_3)_2CCH_3$ [4a], $CH(CH_3)_2$ [4b, 5], $CH_2C(CH_3)_3$ [4c, d], $CH_2Si(CH_3)_3$ [4e], CH_2CH_3 [6], and Table 1.
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[5] Hindered rotation of the $CH(CH_3)_2$ groups in the radical cation of tetraisopropylethene, which we have generated electrochemically at -80°C, follows from the coupling constants of the β-protons: $a_\beta^H = 2.28$ G (2H), 0.4 G (2H); $a_\gamma^H = 0.57$ G (24H).
[6] Hindered rotations of the ethyl groups in the ethenes **1b**, **2b**, and **3b** follow from line-broadening effects in the ^{1}H-NMR spectra. *syn-anti*-Isomers are detectable for **1b** and **2b** below -50 and -115°C, respectively.
[7] **1a** and **2a** were prepared as described by *Rice* et al. [8], **1b**, **2b** and **3a**–**c** according to the method of *Barton* et al. [9]. The *Z*-, *E*-isomers were separated by gas chromatography.
[8] J. E. Rice, Y. Okamoto, *J. Org. Chem. 47* (1982) 4189.
[9] T. G. Back, D. H. R. Barton, M. R. Britten-Kelly, F. S. Guziec, Jr., *J. Chem. Soc. Perkin Trans. 1 1976*, 2079, and references cited therein.
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[11] Hindered rotation of the *tert*-butyl groups in the ethene **3a** follows from the marked broadening of the corresponding ^{13}C-NMR signal at -155°C. Since neither the temperature range of the coalescence nor that of slow exchange was accessible, only an upper limit can be estimated for the barrier. Assuming $\Delta\delta = 100-400$ Hz, ΔG^+ must be less than 5 kcal/mol.
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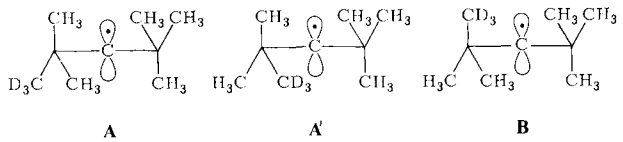
[13] In the case of hindered rotation of the *tert*-butyl groups, only the six protons of the two "axial" methyl groups of the conformations **A** and **A'** lead to splitting into a 1:6:15:20:15:6:1 septet with $a^H = 2.5$ G. The additional ESR spectrum of the conformation **B** is not resolved, since each line of the 1:3:3:1 quartet (2.5 G) of the axial CH_3 group is split into a 1:3:6:7:6:3:1 septet with $a^D = 2.5/\approx 6.5 \approx 0.4$ G, while the line width is 1.7 G.



A **A'** **B**

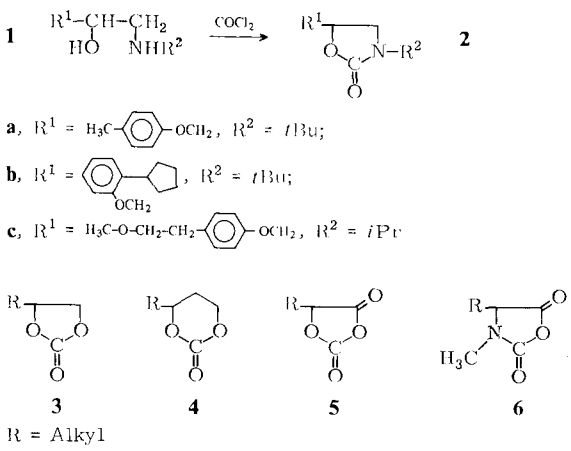
On hindered rotation of the methyl groups only five protons would lead to splitting, since one deuterium of the CD_3 group always adopts a position which would lead to coupling.

[14] The similarity of $3^{\odot\oplus}$ and $4^{\odot\oplus}$ is also reflected in the size of the ESR coupling constants of the γ-protons (2.3 and 2.5 G in the case of $4^{\odot\oplus}$, 2.5-2.9 G in the case of $3^{\odot\oplus}$).

Phosgene as a Reagent for the Enantiomeric Resolution of 1,2- and 1,3-Diols, α-Amino Alcohols, α-Hydroxy Acids, and *N*-Methyl-α-Amino Acids by Gas Chromatography**

By *Wilfried A. König**, *Eberhard Steinbach*, and *Karin Ernst*

Isocyanates have proved to be versatile reagents for the preparation of carbamate, urea, and amide derivatives of chiral hydroxy, amino, and carboxy compounds which can be resolved by gas chromatography[1]. We now report on the use of phosgene as a reagent for enantiomeric resolution. Phosgene-containing solutions react with α-amino alcohols (such as **1**) to give the oxazolidin-2-one **2**[2], with 1,2- and 1,3-diols to give the cyclic carbonates **3** and **4**[3], respectively, with α-hydroxy acids to give the 1,3-dioxolane-2,4-diones **5**[4], and with *N*-methyl-α-amino acids to give the *N*-methyloxazolidine-2,5-diones **6**[5].



1 **2**

a, R^1 = H_3C–⟨○⟩–OCH_2, R^2 = *t*Bu;
b, R^1 = ⟨○⟩(OCH$_2$), R^2 = *t*Bu;
c, R^1 = H_3C–O–CH_2–CH_2–⟨○⟩–OCH_2, R^2 = *i*Pr

3 **4** **5** **6**

R = Alkyl

With 30–50 μL of phosgene solution (20% in toluene) and between 0.1 and 1 mg of starting material in dichloromethane or ether, the reactions afford good yields at room temperature in 30–60 min. When ammonium salts are used, addition of a small amount of 0.5 M NaOH is advantageous. α-Hydroxy acids react particularly well in dioxane in the presence of a trace of pyridine. The derivatives, obtained from racemic compounds, can be readily resolved into their enantiomers by gas chromatography (glass or fused silica capillary columns, stationary phase: polysiloxane XE-60-L-valine-(*R*)-α-phenylethylamide[6]) (Table 1). The derivatization proceeds without racemization.

Aliphatic 1,2- and 1,3-diols (Fig. 1)—frequently used chiral building blocks for the synthesis of natural products[7] and for which various enantioselective synthetic methods have been developed[8]—could previously hardly be resolved into enantiomers by gas chromatography; this could only be achieved with aryl-substituted 1,2-diols via perfluoroacylated derivatives[9]. Diols and α-amino alcohols with additional functional groups can also be resolved as cyclic carbonates and oxazolidin-2-ones, respectively. By this means, racemic tartaric acid and *N*-methylthreonine were resolved after esterification of the carboxy groups with isopropanol and subsequent reaction with phosgene.

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Table 1. Gas chromatographic enantiomer resolution of 1,2- and 1,3-diols, 2-hydroxycarboxylic acids, α-amino alcohols, and *N*-methyl-α-amino acids after derivatization with phosgene. Capillary columns, stationary phase: XE-60-L-valine-(*R*)-α-phenylethylamide.

Racemate	Separation factor α	Column length [m]/ Column temp. [°C]	Enantiomer eluted first
1,2-propanediol [a]	1.021	35/80	*S*
1,2-butanediol	1.017	35/80	*S*
1,2-pentanediol	1.021	35/80	*S*
3-methyl-1,2-butanediol	1.013	35/80	[b]
3,3-dimethyl-1,2-butanediol	1.016	35/80	[b]
1,2-hexanediol	1.026	25/100	*S*
4-methyl-1,2-pentanediol	1.013	35/110	[b]
1,2-octanediol	1.026	25/120	[b]
7-octene-1,2-diol	1.025	25/120	[b]
phenyl glycol	1.031	25/120	*S*
2-ethyl-1,3-hexanediol	1.025 1.018	25/120	[b]
1,3-butanediol	1.018	35/140	*S*
trans-1,2-cycloheptanediol	1.031	25/140	[b]
trans-1,2-cyclooctanediol	1.044	25/140	[b]
trans-1,2-cyclodecanediol	1.031	18/175	[b]
diisopropyl tartrate [c]	1.020	35/145	L
lactic acid	1.015	35/110	L
2-hydroxybutyric acid	1.017	35/110	[b]
2-hydroxyvaleric acid	1.022	35/110	[b]
2-hydroxyisovaleric acid	1.016	35/110	[b]
2-hydroxyhexanoic acid	1.019	35/120	[b]
2-hydroxyisohexanoic acid	1.020	35/120	L
2-hydroxy-3-methylpentanoic acid	1.014	35/120	L
2-hydroxyoctanoic acid	1.035	35/126	[b]
ephedrine	1.040	18/165	(+)
pseudoephedrine	1.047	18/165	(+)
norephedrine	1.026	18/195	[b]
bupranolol (**1a**) [d]	1.025	18/195	*R*
penbutolol (**1b**) [d]	1.025	18/195	*R*
metoprolol (**1c**) [d]	1.031	18/195	*R*
N-methylalanine	1.020	25/100	L
N-methyl-α-aminobutyric acid	1.025	25/100	L
N-methylvaline	1.038	25/100	L
N-methylisoleucine	1.031	25/110	L
N-methylalloisoleucine	1.028	25/110	L
N-methylleucine	1.034	25/110	L
N-methylthreonine [e]	1.049	25/120	L
N-methylallothreonine [e]	1.028	25/120	L
proline	1.038	25/140	D

[a] The diols were kindly supplied by Dr. *K. Günther*, Degussa AG, Hanau. [b] Order of elution was not determined. [c] Separation on XE-60-L-valine (*S*)-α-phenylethylamide. [d] Bupranolol was supplied by Sanol Schwarz-Monheim GmbH, penbutolol by Hoechst, Frankfurt, and metoprolol by Hässle, Gothenburg, Sweden. [e] As isopropyl ester.

For tartaric acid, the resolution on the XE-60-L-valine-(*S*)-α-phenylethylamide phase[6] is better than on the diastereomeric phase. Particularly large separation factors α are obtained for the alicyclic *trans*-1,2-diols (Table 1). For alicyclic *trans*-1,3-diols, cyclic carbonates do not form for steric reasons.

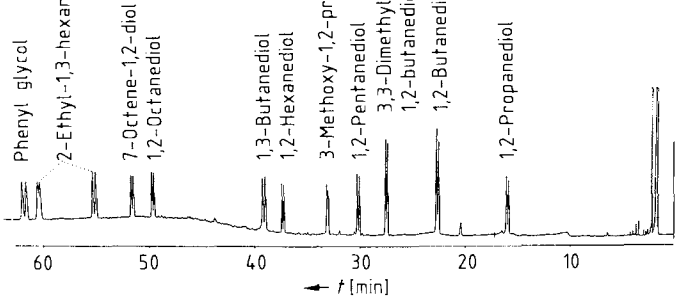

Fig. 1. Enantiomer resolution of the cyclic carbonates of 1,2- and 1,3-diols. 35m fused-silica capillary, coated with XE-60-L-valine-(*R*)-α-phenylethylamide; column temperature 90°C, temperature program 1°C/min up to 110°C, then 2.5°C/min up to 170°C. Carrier gas H_2, 0.9 bar.

Oxazolidine-2-ones from amino alcohols of the ephedrine type are also readily resolvable and configurationally stable derivatives[10]. This also applies to amino alcohols, which have considerable importance as β-receptor blockers in the treatment of cardiac-circulation diseases, but could previously not be resolved[11]. Today, β-blockers are largely used in the form of racemates; however, because of the, in part, extremely different action of the enantiomers the pure enantiomers are sought.

Compared to the derivatives prepared by reaction of isopropyl isocyanate with 2-hydroxy acids or *N*-methyl-α-amino acids[1], those derivatives obtained by reaction with phosgene offer the advantage of considerably higher volatility. Phosgene is therefore an alternative and/or extension to the isocyanates for the derivatization of chiral, polyfunctional compounds for resolution by gas chromatography.

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High-Pressure Phases of KSi, KGe, RbSi, RbGe, CsSi, and CsGe with the NaPb-Type Structure**

By *Jürgen Evers**, *Gilbert Oehlinger*, *Gerhard Sextl*, and *Armin Weiss*

The compounds $SrGe_2$[2], $BaSi_2$ and $BaGe_2$[2], which crystallize in the $BaSi_2$-type structure[1] at normal pressure (NP), are characterized by two unusual properties: (i) their Si or Ge sublattice is reminiscent of the P_4 tetrahedron of white phosphorus, (ii) they are semiconductors[3]. The semimetal sublattice of these phases contains isolated Si_4- or Ge_4-tetrahedra of three-bonded atoms which can be formulated ionically as

$\geqslant Si:^{\ominus}$ and $\geqslant Ge:^{\ominus}$

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with fully occupied octets; they contain the same number of valence electrons as phosphorus. Fully occupied valence shells confer non-metallic properties on the solid species.

At high pressures and temperatures (e.g. 4 GPa, 1000 °C) the isolated tetrahedra in $SrGe_2$[4], $BaSi_2$[5] and $BaGe_2$[6] can be transformed into layer or three-dimensional network arrays of three-bonded atoms, with concomitant loss of semiconducting properties. This transformation is most impressive in the case of $BaGe_2$; its "high pressure/high temperature (HPHT) phase", which can be kept in the metastable state at normal pressure, is superconducting (critical temperature: 4.9 K)[7].

The structures of the compounds formed from the alkali metals K, Rb and Cs and the Group IV elements Si, Ge, Sn, and Pb also consist of isolated tetrahedra at normal pressure. The silicides and germanides of K, Rb and Cs crystallize in the cubic KGe-type structure[8], the corresponding stannides and plumbides[9] in the tetragonal NaPb-type structure[10]. In this paper we report on transformations of the silicides and germanides at high pressures and high temperatures.

The cubic NP-phases were synthesized from the elements under argon. The alkali metals (10% excess) were fused together with semiconductor silicon (or germanium) in a corundum crucible. Due to the considerably high vapor pressure of the alkali metals at the synthesis temperature (650—750 °C), the corundum crucible was heated in a copper-sealed iron container. Both the alkali metals and their silicides and germanides are extremely sensitive to air and moisture; therefore all operations with open crucibles had to be carried out in a glove box under very pure argon. The HPHT experiments were performed in boron nitride crucibles in a Belt type apparatus at 4 GPa and 600—700 °C.

We were able to quench six high-pressure (HP) phases of the alkali metal silicides and germanides to ambient conditions. When heated to about 400 °C at NP, these phases were transformed into the thermodynamically stable phases with the cubic KGe-type structure in exothermic reactions. Chemical analyses of the new phases of KSi gave no indication of a change in the 1:1 composition. The pycnometrically determined densities and those calculated from X-ray data were in good agreement. All six HP-phases are isotypic. Their X-ray powder diagrams (Debye-Scherrer method, $Cu_{K\alpha}$, 114.6 mm) can be indexed tetragonally. Intensities of the reflections were calculated with the "Lazy Pulverix"[11] program (position parameters: single-crystal data of KSn[9]) and found to be in good agreement with the NaPb-type structure.

Table 1. Lattice parameters of the tetragonal NaPb-type phases AB (A = K, Rb, Cs; B = Si, Ge, Sn, Pb).

Compound	Phase [a]	a Axis [pm]	c Axis [pm]	Axial ratio c/a
KSi	HP	1057	1710	1.62
KGe	HP	1069	1737	1.62
KSn	NP [9]	1142	1857	1.63
KPb	NP [9]	1150	1876	1.63
RbSi	HP	1083	1758	1.62
RbGe	HP	1104	1787	1.62
RbSn	NP [9]	1171	1909	1.63
RbPb	NP [9]	1184	1942	1.63
CsSi	HP	1123	1834	1.63
CsGe	HP	1138	1850	1.63
CsSn	NP [9]	1219	1987	1.63
CsPb	NP [9]	1226	1999	1.63

[a] HP = high-pressure phase, NP = normal-pressure phase; the standard deviations of the lattice parameters in the HP-phases are a: ±3 pm, c: ±5 pm.

In Table 1 the a and c axes of the six new phases of the silicides and germanides of potassium, rubidium and cesium are compared with those of the known NP-phases[9] of the corresponding stannides and plumbides. The c/a ratio of all twelve phases has a constant value of 1.62—1.63, convincingly indicating a geometrical relationship as for the NaPb-type structure. This value corresponds to:

$$c_{tetr.}/a_{tetr.} \approx (0.96 a_{cub}\sqrt{2})/(0.96 \cdot 0.5 a_{cub}\sqrt{3}) \approx \tfrac{2}{3}\sqrt{6} \approx 1.63$$

In comparison to the cubic KGe-type structure of the NP-phases, the HP-phases are about 4% more densely packed. Whether this increase in density is associated with a slight increase in the coordination numbers must remain open until an accurate determination of the positional parameters has been carried out. Thus, isolated tetrahedra are still stable in the HP-phases of the alkali metal silicides and germanides up to 4 GPa. A transformation into layer or network arrays is probably rendered difficult here because of the metal content being twice as high as in the alkaline earth metal silicides and germanides.

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Hydridoplatinum(II) Complexes with Phosphites and Phosphonites and their Reactions with Methyl Acrylate**

By *Werner R. Meyer* and *Luigi M. Venanzi**

While hydrido complexes of the type *trans*-$PtHXL_2$ (L = tertiary phosphane, X = halide) have been known for a long time[1], the analogous compounds with $L = P(OR)_3$, $PR'(OR)_2$, or $PR'_2(OR)$ have not been reported hitherto, although $PtHCl[P(OPh)_3]_2$ has been postulated as a co-catalyst for the isomerization of randomly unsaturated to conjugated compounds[2]. We report here the facile synthesis of *trans*-$PtHCl[P(OMe)_3]_2$ **1**, *trans*-$PtHCl[PMe(OMe)_2]_2$ **2**, and their reactions with $CH_2{=}CH{-}CO_2Me$.

Compound **1** is formed in high yield by allowing *cis*-$PtCl_2[P(OMe)_3]_2$[3] to react with $NaBH_4$ in acetonitrile. The colorless solid product ($\nu(Pt{-}H) = 2050\ cm^{-1}$) is obtained

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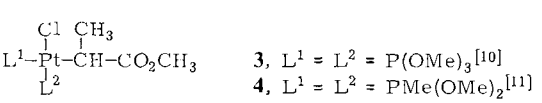
from the reaction medium by addition of diethyl ether. As a dry solid, complex **1** decomposes rapidly forming a mixture of products in which *cis*-$PtCl_2[P(OMe)_3]_2$ and $Pt[P(OMe)_3]_4$[4] can be identified from their ^{31}P-NMR parameters. However, solutions of compound **1** are stable at room temperature for several hours even in air.

Characterization of compound **1**[5] follows from its NMR spectra[6]. While the ^1H-NMR data of the hydrido ligand are very similar to those of *trans*-$PtHCl[PEt_3]_2$[7], the ^{31}P-NMR data are typical of $P(OR)_3$-complexes, i.e. low field $\delta^{31}P$ values and large $^1J_{P\text{-}Pt}$ values[8].

The thermally more stable **2** can be prepared similarly[9].

Compounds **1** and **2** react rapidly with $CH_2{=}CH{-}CO_2Me$ in acetone at room temperature to give the insertion products **3** and **4**, respectively.



3, $L^1 = L^2 = P(OMe)_3$[10]
4, $L^1 = L^2 = PMe(OMe)_2$[11]

There are three notable features to this insertion reaction:

1) It proceeds smoothly, even though chloride is coordinated to the platinum atom in contrast to *trans*-$PtHCl[PEt_3]_2$, which does not react with methyl acrylate[12].
2) Complexes **3** and **4** have the usual *cis*-geometry, but do not rearrange to their respective *trans*-isomers as found for the corresponding PEt_3-complexes[13].
3) Only a branched alkyl chain is formed, irrespective of the nature of solvent used for this reaction, in contrast to the behavior of the PEt_3-complexes where the branched is always accompanied by the linear isomer and the ratio of these two forms is solvent-dependent[14].

In summary, hydridoplatinum(II) complexes with phosphites or phosphonites can be obtained and show very high reactivity and regioselectivity towards alkene insertion. Thus, they could prove to be useful reagents and/or catalysts for organometallic reactions.

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CAS Registry numbers:
1, 90838-78-1; **2**, 90838-79-2; **3**, 90838-80-5; **4**, 90838-81-6; *cis*-$PtCl_2[P(OMe)_3]_2$ 28374-51-8; *cis*-$PtCl_2[PMe(OMe)_2]_2$ 90838-82-7

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[6] ^1H-NMR (90 MHz) in [D$_6$]acetone: $\delta(CH_3) = 3.88$ (pseudotriplet), $|^3J_{P-H} + {}^5J_{P-H}| = 14$ Hz; $\delta(PtH) = -16.34$, $^1J_{Pt-H} = 1211$ Hz, $^2J_{P-H} = 18$ Hz; $^{31}P\{^1H\}$-NMR (36.43 MHz, H_3PO_4 ext.), in [D$_6$]acetone: $\delta = 126$, $^1J_{Pt-P} = 4661$ Hz; $^{195}Pt\{^1H\}$-NMR: (53.53 MHz, K_2PtCl_6 ext. standard) in CD_2Cl_2: $\delta = -4956.5$ (t).
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[9] IR: $\nu(Pt-H) = 2060$ cm^{-1}; ^1H-NMR (90 MHz) in benzene: $\delta(OCH_3) = 3.62$ (pseudotriplet) $|^3J_{P-H} + {}^5J_{P-H}| = 7$ Hz, $\delta(CH_3) = 1.68$–1.93 (complex multiplet); $\delta(Pt-H) = -15.35$, $^1J_{Pt-H} = 1255$ Hz, $^3J_{P-H} = 9.4$ Hz; ^{31}P (36.43 MHz, H_3PO_4 ext. standard) in [D$_6$]acetone: $\delta = 160$, $^1J_{Pt-P} = 3673$ Hz; determination of the Pt:P:Cl ratio gives 1:1.95:1.04.
[10] IR: $\nu(C{=}O) = 1740$ cm^{-1}, $\nu(Pt-Cl) = 310$ cm^{-1}. ^1H-NMR (90 MHz) in CD_2Cl_2: $\delta(POCH_3) = 3.70$, 3.80; $\delta(PtCHCH_3COOCH_3) = 1.15$ (ddd), $^3J_{H-H} = 7$ Hz, $^4J_{P2-H} = 1$ Hz, $^4J_{P1-H} = 14$ Hz, $^3J_{Pt-H} = 16$ Hz; $\delta(PtCHCH_3COOCH_3) = 3.50$ (s); $^{13}C\{^1H\}$-NMR (62.87 MHz) in CD_2Cl_2 (multiplicity of the resonances in an "off-resonance" mode are shown in parentheses): $\delta(PtCHCH_3COOCH_3) = 28.79$ (t), $^1J_{C-Pt} = 460.8$ Hz, $^2J_{C-P1} = 4.7$, $^2J_{C-P2} = 129.4$ Hz; $\delta(PtCHCH_3COOCH_3) = 16.02$ (q), $^2J_{C-P} = 7.4$ Hz, $^3J_{C-Pt} = 22.2$ Hz; $\delta(PtCHCH_3COOCH_3) = 50.23$ (q); $\delta(PtCHCH_3COOCH_3) = 180.44$ (s), $^2J_{C-Pt} = 42.0$ Hz, $^3J_{C-P} = 6.7$ Hz. ^{31}P-NMR (36.43 MHz, H_3PO_4 ext. standard) in [D$_6$]acetone: $\delta(P_1) = 119.3$, $^1J_{P1-Pt} = 3068$ Hz; $\delta(P_2) = 85.6$, $^1J_{P2-Pt} = 6248$ Hz; $^2J_{P-P} = 40$ Hz; determination of the Pt:P:Cl ratio gives 1:1.94:1.05.
[11] IR: $\nu(C{=}O) = 1700$ cm^{-1}. ^1H-NMR (90 MHz) in CD_2Cl_2: $\delta(POCH_3) = 3.43$, 3.61 (complex multiplet), $\delta(PtCHCH_3COOCH_3) = 1.02$ (ddd), $^3J_{H-H} = 6$ Hz, $^4J_{P2-H} = 1$ Hz, $^4J_{P1-H} = 9$ Hz, $^3J_{Pt-H} = 15$ Hz; $\delta(PtCHCH_3COOCH_3) = 3.34$ (s); $\delta(P_1-CH_3) = 1.61$, $^2J_{P1-CH_3} = 9$ Hz, $^3J_{Pt-P1CH_3} = 3$ Hz; $\delta(P2-CH_3) = 1.58$, $^2J_{P2-CH_3} = 7$ Hz, $^3J_{Pt-P2CH_3} = 9$ Hz; $^{13}C\{^1H\}$-NMR (62.87 MHz) in CD_2Cl_2: $\delta(PtCHCH_3COOCH_3) = 28.31$, $^1J_{C-Pt} = 458.4$ Hz, $^2J_{C-P1} = 4.9$ Hz, $^2J_{C-P2} = 108.5$ Hz; $\delta(PtCHCH_3COOCH_3) = 15.9$, $^3J_{C-P} = 6.0$ Hz (tentative assignment); $\delta(PtCHCH_3COOCH_3) = 180.99$, $^2J_{C-Pt} = 40.3$ Hz, $^3J_{C-P} = 4.9$ Hz; $\delta(PtCHCH_3COOCH_3) = 50.19$; ^{31}P-NMR (36.43 MHz, H_3PO_4) in [D$_6$]acetone: $\delta(P_1) = 150$, $^1J_{P1-Pt} = 2623$ Hz; $\delta(P_2) = 117$, $^1J_{P2-Pt} = 5540$ Hz; $^2J_{P-P} = 27$ Hz; determination of the Pt:P:Cl ratio gives 1:1.98:1.02.
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Synthesis and Determination of the Absolute Configuration of (+)-Delesserine, a Metabolite of the Red Marine Alga *Delesseria sanguinea* (Lamouroux)

By *Dieter Seebach**, *Matthias Dust*, *Reto Naef*, and *Markus Bänziger*

Delesserine **6** is a γ-lactone isolated from the algae *Delesseria sanguinea* (Lamouroux). The relative configuration was determined by an X-ray crystal structure analysis[1], Aqueous extracts of *Delesseria sanguinea*, an alga occurring on the European Atlantic coast, are powerful anticoagulants for human blood[2].

We describe here a short synthesis of enantiomerically pure, natural delesserine **6** starting from diethyl (*R,R*)-(+)-tartarate[3] and demonstrate the relationship of delesserine to the (L)-series of C_6-carbohydrates, which had previously only been conjectured.

The key reaction in the synthesis is the addition of the lithium enolate of the phenyl lactic acid derivative **1** to the aldehyde **2** [acetonide and benzyl-protected (L)-threose], which was synthesized in four steps from diethyl tartarate[3–5]. Information about the formation of this C–C linkage, which completes the assembly of the carbon skeleton, and about further reactions is given in Scheme 1. Alcohol **3** (four diastereomers) was oxidized directly, without isolation, to the β-keto ester **4**, which was present in two forms epimeric at the α-C atom. After hydrolysis of the acetonides, a 1:2 mixture of lactones **5a** and **5b** was obtained, from which isomer **5a** could be isolated as ana-

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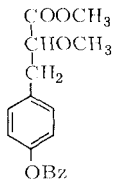
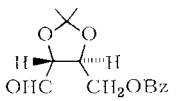
lytically pure crystals. After debenzylation of **5a** via hydrogenation, delesserine **6**, which exists in solution as an equilibrium mixture of the bicyclic and monocyclic forms



1



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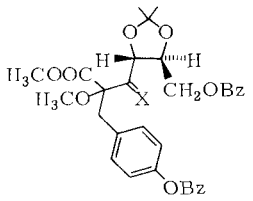

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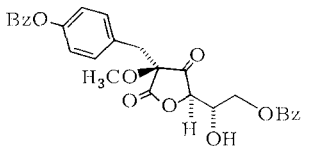
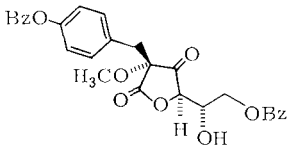
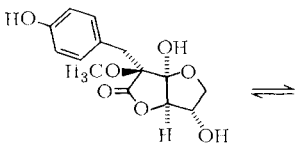
4, X = O



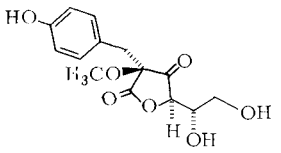
5a



5b



6a



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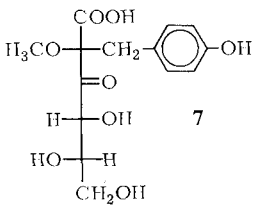

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Scheme 1. Bz = benzyl. **1**: From methyl methoxyacetate and 4-benzyloxybenzyl bromide with lithium diisopropylamide (LDA) in tetrahydrofuran (THF), −75 °C, yield 86%.—**2**: In four steps from diethyl (+)-tartarate[4], 40%.—**3**: From **1** (LDA in THF, −75 °C) and **2**.—**4**: By Swern-oxidation [8] of **3** (dimethyl sulfoxide (DMSO), $(COCl)_2$, Et_3N, in CH_2Cl_2); 62% based on **2**.—**5**: By hydrolysis of the acetonide protecting group (TsOH, MeOH) 91%. Separation of the two diastereomers by crystallization from ether/pentane; **5a** (35% of the mixture) crystallized (m.p. 144 °C), **5b** (65% of the mixture) remains in the mother liquor and is isolated as an oil.—**6**: From **5a** by debenzylation with Pd/C in MeOH; 90% colorless, non-crystalline powder, m.p. ≈ 105 °C, $[\alpha]_D^{20} = +44$ ($c = 0.72$, MeOH) [6] (natural product: +36 [1]); ratio **6a**/**6b** (5 mg/mL CD_3OD): 63/37 (^{1}H-NMR); ^{13}C- and ^{1}H-NMR data of **6a** and **6b** agree with the values given in [1].

6a and **6b**, was obtained. The identity of **6** was proven by comparison of the sign and magnitude of its optical rotation and ^{1}H-NMR data with the values reported in the literature[1,6]. Delesserine **6** possesses no anticoagulant properties in the Quick test[7].

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CAS Registry numbers:
1, 74649-77-7; **2**, 81028-12-8; **3** (isomer 1), 90866-60-7; **3** (isomer 2), 90899-80-2; **3** (isomer 3), 90899-81-3; **3** (isomer 4), 90899-82-4; **4** (isomer 1), 90858-88-1; **4** (isomer 2), 90899-52-8; **5a**, 90858-89-2; **5b**, 90899-53-9; **6a**, 82198-78-5; **6b**, 90899-54-0; methyl methoxyacetate, 6290-49-9; 4-benzyloxybenzyl bromide, 5544-60-5

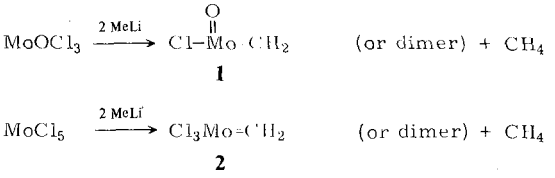
[1] J. C. Yvin, A.-M. Chevolot-Magueur, L. Chevolot, J.-Y. Lallemand, P. Potier, J. Guilhem, *J. Am. Chem. Soc. 104* (1982) 4497.
[2] H. Elsner, A. Liedmann, K. Oppers, *Naunyn-Schmiedebergs Arch. Exp. Pathol. Pharmakol. 190* (1938) 510.
[3] D. Seebach, E. Hungerbühler in R. Scheffold: *Modern Synthetic Methods 1980*, Vol. 2, Salle+Sauerländer, Frankfurt am Main+Aarau 1980.
[4] E. Hungerbühler, D. Seebach, *Helv. Chim. Acta 64* (1981) 687.
[5] T. Mukaiyama, K. Suzuki, T. Yamada, *Chem. Lett. 1982*, 929.
[6] The debenzylation product of **5b**, *epi*-delesserine, has the rotation $[\alpha]_D^{20} = -2.7$ under the same conditions.
[7] We wish to thank Dr. *D. Hauser* (Sandoz AG, Basel) for this test.
[8] A. J. Mancuso, S.-L. Huang, D. Swern, *J. Org. Chem. 43* (1978) 2480.

Carbonyl Olefinations with Methylenemolybdenum Reagents in Aqueous or Ethanolic Media**

By *Thomas Kauffmann**, *Petra Fiegenbaum*, and *Raphael Wieschollek*

Among the known transition metal reagents that have been used for carbonyl olefinations[2,3], the molybdenum complexes first reported by us[2c,d] deserve special attention, since they are the most easily accessible and are comparable in their carbonyl selectivity to the titanium-containing alkylating reagents[4].

We report herein that the Mo-compounds **1** and **2** accessible according to Scheme 1 are—other than the titanium-containing Tebbe-reagent[2a] and the structurally related Zr-reagents of *Schwartz* et al.[2b]—suitable for carbonyl olefination in aqueous or ethanolic solvents[5], which could prove advantageous in the case of hydrophilic substrates.



Scheme 1.

The reagent prepared in anhydrous tetrahydrofuran (THF) (5 mmol in 50 mL) according to Scheme 1 is treated with the carbonyl compound dissolved or suspended in water, ethanol/water mixture, or ethanol (in each case ca. 20 mL) (Table 1). If this is carried out at −70 °C, the mixture is allowed to warm to room temperature within 12 h; if the addition is carried out at 0 °C, then the mixture is kept at this temperature for 1 h.

Reactions with **1**: The yields of alkene (Table 1) on addition of the substrate in ethanol or ethanol/water at −70 °C are practically the same as on addition of the substrate in anhydrous THF, with one exception: for some unknown reason **1** reacts better with benzaldehyde in the presence of water or ethanol. Thus, as a rule, the carbonyl olefination is more rapid than a replacement of the Cl substituents in **1** by OEt or OH. If, however, water is added at 0 °C there is a distinct loss in reactivity.

Reactions with **2**: In ethanol or aqueous THF the yields of alkene are substantially lower than in anhydrous THF (Table 1). The drastic reduction in yield of alkene on addi-

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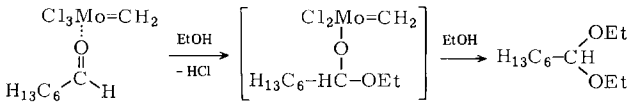
[**] Transition Metal-Activated Organic Compounds, Part 15. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.—Part 14: [1].

tion of ethanol in the reaction with heptanal can be ascribed, in part, to the fact that its diethyl acetal **4** (13%) is formed. Since **4** is undoubtedly formed via a semiacetal-like intermediate and a lot of heptanal is recovered after hydrolysis, presumably some of the heptanal of the carbonyl olefination is removed by formation of **3**.



3 **4**

Table 1. Carbonyl olefinations in THF with added EtOH, H_2O or EtOH/H_2O. Molar ratio of reagent: carbonyl compound = 2:1, in competition reactions 2:1:1. Yields in brackets refer to the reaction in anhydrous THF.

Reagent	Carbonyl compound	Added solvent	T [°C]	Yield [%] Alkene [a]	Recovered carbonyl compound
1	Ph–CHO	EtOH	−70	90 (20)	1 (4)
1	Ph–CHO	H_2O	0	50	22
1	4-MeO–C_6H_4–CHO	EtOH	−70	92 (93)	0 (0)
1	4-MeO–C_6H_4–CHO	EtOH/H_2O(4:6)	−70	83	5
1	4-MeO–C_6H_4–CHO	H_2O	0	55	16
1	C_6H_{13}–CHO	EtOH	−70	23 (25)	0 (0)
1	Ph–CO–Me	EtOH	−70	48 (49)	47 (39)
1	4-MeO–C_6H_4–CHO + Ph–CO–Me	EtOH	−70	62/1 [b] (63/1)	12/87 (10/60)
2	Ph–CHO	EtOH	−70	36 (65)	46 (30)
2	Ph–CHO	H_2O	0	31	61
2	4-MeO–C_6H_4–CHO	EtOH	−70	41 (84)	56 (3)
2	C_6H_{13}CHO	EtOH	−70	10 (65)	59 (25)

[a] Referred to carbonyl compound used. Determined gas-chromatographically. [b] Preferred olefination of the aldehyde.

Stability of **1** and **2** toward protic solvents: We treated the THF solution of these reagents with 20 mL ethanol or water, added a carbonyl compound after prescribed times, and determined the yields of alkene. As shown in Figure 1, **1** and **2** are still rather active after 30 min at 0 °C and 30 min at −70 °C, respectively, despite a large excess of water (molar ratio: H_2O:**1** = 220:1) or ethanol (C_2H_5OH:**2** = 70:1). According to the activity curve a new stable species is formed from **2**.

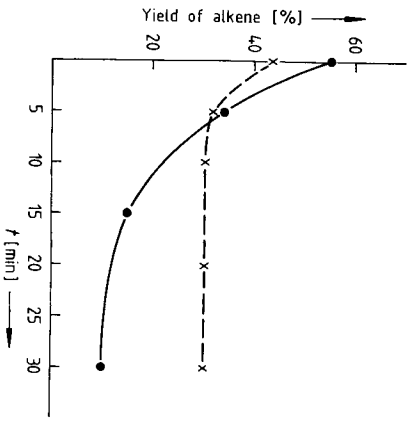
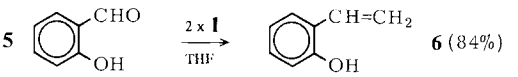


Fig. 1. Loss of reactivity of **1** (——) and **2** (- - - -) on addition of H_2O or ethanol, respectively; reactions of **1** with 4-MeO–C_6H_4–CHO at 0 °C and of **2** with Ph–CHO at −70 °C, respectively. Points on the ordinates: protic solvent and carbonyl compound given simultaneously.



6 (84%)

Since **1** and **2** are relatively insensitive towards compounds containing OH-groups, it was expected that hydroxyaldehydes can be readily olefinated with these reagents. The reaction **5** → **6** does indeed proceed quite smoothly in anhydrous THF[6].

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CAS Registry numbers:
1, 84809-63-2; **2**, 84809-61-0; **4**, 688-82-4; **5**, 90-02-8; **6**, 695-84-1; $MoOCl_3$, 13814-74-9; $MoCl_5$, 10241-05-01; PhCHO, 100-52-7; 4-$MeOC_6H_4CHO$, 123-11-5; $CH_3(CH_2)_5CHO$, 111-71-7; $PhC(O)CH_3$, 98-86-2; $PhCH=CH_2$, 100-42-5; 4-$MeC_6H_4CH=CH_2$, 637-69-4; $CH_2=CH(CH_2)_5CH_3$, 111-66-0; $PhC(CH_3)=CH_2$, 98-83-9

[1] Th. Kauffmann, M. Bisling, *Tetrahedron Lett. 25* (1984) 293.
[2] a) F. N. Tebbe, G. W. Parshall, G. S. Reddy, *J. Am. Chem. Soc. 100* (1978) 3611; b) F. W. Hartner, Jr., J. Schwartz, *ibid. 103* (1981) 4979; c) Th. Kauffmann, B. Ennen, J. Sander, R. Wieschollek, *Angew. Chem. 95* (1983) 237; *Angew. Chem. Int. Ed. Engl. 22* (1983) 244; d) Th. Kauffmann, G. Kieper, *ibid. 96* (1984) 502 and *23* (1984) 532.
[3] The carbonyl olefinations with a Nb- and a Ta-reagent described by R. R. Schrock, *J. Am. Chem. Soc. 98* (1976) 5399, gave poor yields.
[4] M. T. Reetz, *Top. Curr. Chem. 106* (1982) 1; D. Seebach, B. Weidmann, L. Widler in R. Scheffold: *Modern Synthetic Methods 1983*, Salle, Frankfurt 1983.
[5] Carbonyl olefinations in aqueous medium were first observed by R. Wieschollek (Universität Münster).
[6] Procedure: **6**: Dissolution of $MoCl_5$ (1.37 mg, 5 mmol) in anhydrous THF at room temperature leads (within 2 h) to formation of the complex $(THF)_2MoOCl_3$ [7]. The solution is stirred with 10 mmol MeLi (ca. 1.5 M in ether) at −70 °C for 1.5 h and then treated with 305 mg (2.5 mmol) *o*-hydroxybenzaldehyde. The mixture is allowed to warm to room temperature within 12 h, hydrolyzed with 20 mL water, and rendered neutral with $NaHCO_3$. The aqueous phase is extracted three times with 20 mL hexane. The combined organic phases are shaken with a $K_4[Fe(CN)_6]$ solution (2 g in 20 mL H_2O) to give a water-soluble Mo-complex, washed twice with water, and dried. After evaporation to dryness, the alkene is separated by column chromatography (silica gel, 13 × 4 cm, $CHCl_3$); yield 228 mg (76%).
[7] C. A. McAuliffe, A. Werfali, *Inorg. Chim. Acta 60* (1980) 87.

Selective Synthesis of Carbonyl Olefinating or Alkylating Reagents from $MoCl_5$ and MeLi by Changing the Solvent or the Rate of Addition of MeLi**

By *Thomas Kauffmann** and *Gudrun Kieper*

Reaction of methyllithium (MeLi) with $MoCl_5$, $(EtO)_3MoCl_2$ or $O=MoCl_3$ leads to the formation of carbonyl olefinating reagents[1,2]. We have now found, in the case of MeLi and $MoCl_5$, that the rate of addition of MeLi and the solvent have a surprisingly marked influence on the product pattern.

Reactions in tetrahydrofuran (THF): When a solution of 3 or 4 mol equivalents of MeLi in diethyl ether (ca. 1.5 M solution) is added dropwise and *slowly* (1 drop per 7–10 s) to a solution of $MoCl_5$ (5 mmol) in THF (ca. 40 mL) under argon at −70 °C and the mixture is kept at this temperature

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[**] Transition Metal Activated Organic Compounds, Part 16. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.—Part 15: [1].

for a further 2—4 h, in each case an *olefinating reagent* is formed, which we formulate as **1** and **2** (or dimers thereof), respectively. Both compounds react with benzaldehyde or 4-methoxybenzaldehyde to give alkenes in good yields (Table 1). In competition reactions with 4-methoxybenzaldehyde/acetophenone the reagent **1** olefinates practically only the aldehyde.

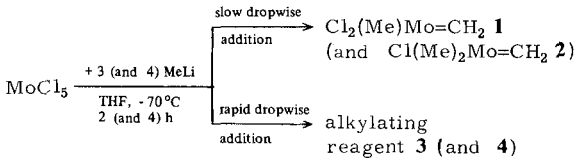


Table 1. Olefinations with **1** and **2**.

Reagent	Carbonyl compound	Mol. ratio Reagent/Substrate	Solvent	Yield [%] [a] Alkene	Alcohol	Recovered carbonyl compound
1	Ph–CHO	2:1	THF	71	0.2	16
1	Ph–CHO	2:1	Et_2O	92	0	0.4
2	Ph–CHO	2:1	THF	36	19	2
2	Ph–CHO	2:1	Et_2O	82	3	3
1	Ph–CO–Me	2:1	THF	34	0	61
2	Ph–CO–Me	2:1	Et_2O	42	0	56
1	4-MeO–C_6H_4–CHO + Ph–CO–Me	2:1:1	THF	58 [b] / 1	0	37 / 90
1	4-MeO–C_6H_4–CHO + Ph–CO–Me	2:1:1	Et_2O	95 [b] / 2	0	2 / 97

[a] Referred to carbonyl compound used. Determined gas-chromatographically. [b] Preferred olefination of the aldehyde.

If the MeLi solution is added *rapidly* (1 drop per second) to the solution of $MoCl_5$ in THF under otherwise the same conditions and the mixture is kept at −70 °C for 2—4 h, the *alkylating reagents* **3** and **4**, respectively, are formed, of which **4** is the most reactive since it also reacts with ethyl butyrate (Table 2). The high reactivity of **4** is likewise reflected in the low selectivity of the competition reaction with aldehyde/ketone.

Table 2. Alkylations with **3** and **4** in THF.

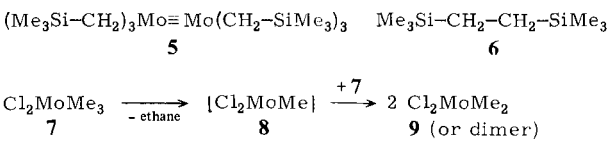
Reagent	Carbonyl compound	Mol. ratio Reagent/Substrate	Yield [%] [a] Alcohol	Alkene	Recovered carbonyl compound
3	Ph–CHO	2:1	86	1	0.4
4	Ph–CHO	2:1	91	0.2	1
4	Ph–CHO	1:1	81	4	1
4	C_6H_{13}–CHO	2:1	75	1	0.2
3	Ph–CO–Me	2:1	30	1	60
3	C_3H_7–COOEt	2:1	0 [b]	0	91
4	C_3H_7–COOEt	2:1	51 [b]	0	30
3	Ph–CN	2:1	0	—	97
4	Ph–CN	2:1	0	—	83
4	4-MeO–C_6H_4–CHO + Ph–CO–Me	2:1:1	87 / 91	3 / 1	0 / 0.3
4	C_6H_{13}–CHO + Et–CO–Et	2:1:1	77 / 95	1 / 0	0 / 0

[a] Referred to substrate used, determined gaschromatographically. [b] Alcohol C_3H_7–C(OH)Me_2; methyl propyl ketone is not found.

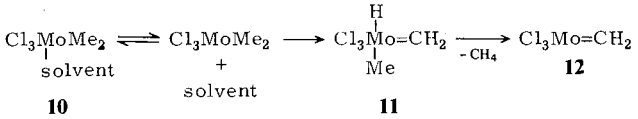
The methylations cannot be ascribed to unconsumed MeLi, since, before addition of the electrophile, stirring of the mixture at −70 °C was prolonged in each case (2—4 h) until the Gilman test with *Michlers* ketone was negative and attack of benzonitrile was no longer possible.

Reactions in diethyl ether: When $MoCl_5$ is allowed to react with 3 mol equivalents of MeLi in diethyl ether instead of in THF the olefinating reagent **1** is formed in each case, irrespective of whether the MeLi is added slowly or rapidly (Table 1). On the other hand, for some unexplained reason the olefinating reagent **2** is obtained in diethyl ether only on slow addition of the MeLi solution.

Mechanistic interpretation: Since $MoCl_5$ reacts with 5.5 mol equivalents of trimethylsilylmethylmagnesium chloride to give the Mo^{III} compound **5** (isolated yield 15%)[3] with formation of **6** (ca. 30%)[4], presumably the trimethyl compound **7** was formed on *rapid* addition of MeLi to $MoCl_5$ (3:1) in THF and reduced by ethane-elimination to the Mo^{III} compound **8**. The yield of ethane, however, is only ca. 50%[5], thus indicating the likelihood of disproportionation of **8** with any **7** that is still present to give the Mo^{IV} compound **9** (hypothetical structure of reagent **3**).



On *slow* addition of MeLi to $MoCl_5$ (3:1) in THF there is sufficient time for the initial product of methylation to be converted with evolution of methane into **12**, which is methylated by excess MeLi into **1** or **2**. If the reaction path **10** → **11** → **12** is assumed for the formation of the



Mo=C double bond, then it is understandable that this is slower in THF than in diethyl ether, which, as the weaker donor (solvent) is more susceptible to coordination.

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[1] Th. Kauffmann, P. Fiegenbaum, R. Wieschollek, *Angew. Chem. 96* (1984) 500; *Angew. Chem. Int. Ed. Engl. 23* (1984) 531.
[2] Th. Kauffmann, B. Ennen, J. Sander, R. Wieschollek, *Angew. Chem. 95* (1983) 237; *Angew. Chem. Int. Ed. Engl. 22* (1983) 244; *Angew. Chem. Suppl. 1983*, 222.
[3] W. Mowat, A. Shortland, G. Yagupsky, N. J. Hill, M. Yagupsky, G. Wilkinson, *J. Chem. Soc. Dalton Trans. 1972*, 533. See also R. A. Andersen, M. H. Chisholm, J. F. Gibson, W. W. Reichert, I. P. Rothwell, G. Wilkinson, *Inorg. Chem. 20* (1981) 3934.
[4] Th. Kauffmann, H. Böcker, unpublished.
[5] Even in the reaction of $MoCl_5$ with two mol equivalents of phenyllithium only ca. 50% of the product of reductive elimination (diphenyl) was obtained.

^{25}Mg-NMR: A Method for the Characterization of Organomagnesium Compounds, their Complexes, and Schlenk Equilibria

By *Reinhard Benn**, *Herbert Lehmkuhl*, *Klaus Mehler*, and *Anna Rufińska*

Although organomagnesium compounds are exceedingly important in preparative chemistry, until now ^{25}Mg-NMR data have only been available for ionic compounds and biological systems[1]. In the course of our investigations of the metal resonances and syntheses of and with organomagnesium compounds[2], we have studied such compounds using ^{25}Mg-NMR and, as far as we are aware, determined the range of their chemical shifts for the first time. We show here, that ^{25}Mg chemical shifts and line widths ($W_{1/2}$) can be used to clarify the multiple bonding, coordination, and association behavior of organomagnesium compounds, and report our studies of methyl-, ethyl-, allyl-, cyclopentadienyl(Cp)magnesium derivatives and of the Schlenk equilibria of organomagnesium halides.

The compounds R_2Mg, RMgHal (R = alkyl, aryl) and $MgBr_2$ are monomeric in tetrahydrofuran (THF) over a wide range of concentrations[3]. The $\delta(^{25}Mg)$ values of these compounds lie between 0 and +100 (Fig. 1, Table 1). The signals of CpMg derivatives lie outside this range.

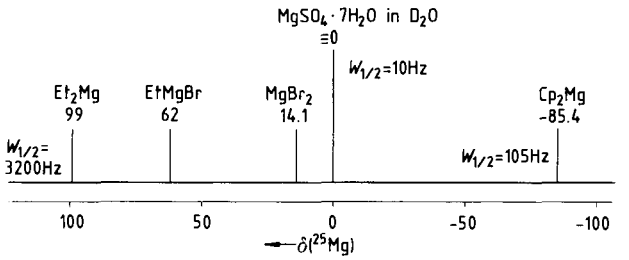

Fig. 1. Range of chemical shifts for ^{25}Mg derivatives. For details, see text and Table 1.

Table 1. ^{25}MgBr parameters of some magnesium compounds [a].

Mg Comp.	Solvent [b]	c [mol·L^{-1}]	$\delta(^{25}Mg)$	$W_{1/2}$ [Hz]	$\delta(^{13}C)$ [b]
Et_2Mg **1**	THF	1.78	99.2	3200	—
$(C_4H_7)_2Mg$ **2** [c]	THF	1.20	70.4	2000	—
MeMgBr **3**	THF	1.63	67.8	1900	—
EtMgBr **4**	THF	1.26	56.2 [d]	1100 [d]	—
$(C_3H_5)MgBr$ **5** [e]	THF	1.00	29.7	1000	—
$MgBr_2$ **6**	THF	0.24	13.9	36	—
$Mg(acac)_2$ **7**	THF	0.29	6.3	650	—
Cp_2Mg·TMED **8**	TMED	0.03	−25.8	50	103.9
CpMgBr **9**	THF	1.51	−26.8	60	105.7
Cp_2Mg·TMBD **10**	toluene	0.65	−31.0	140	105.3/108.5 [f]
Cp_2Mg·nTHF **11**	THF	1.34	−33.8	90	105.8
$(CpMgBr·OEt_2)_2$ **12**	toluene	0.81	−37.9	140	106.5
Cp_2Mg·dioxane **13**	dioxane	0.01	−48.5	~300	105.8
Cp_2Mg·DME **14**	DME	0.30	−49.4	75	105.2
Cp_2Mg·nPMe_3 **15**	PMe_3	0.13	−60.9	220	105.7
Cp_2Mg·nOEt_2 **16**	Et_2O	1.45	−75.3	150	106.9
Cp_2Mg **17**	toluene	0.75	−85.4	105	107.7

[a] At 24.49 MHz (400.134 MHz (^{1}H)), T = 310 K. External standard: $MgSO_4·7H_2O$ in D_2O (0.18 M): $\delta(^{25}Mg) \equiv 0$, $W_{1/2}$ = 10 Hz [4]. Abbreviations: THF = tetrahydrofuran; TMED = 1,2-bis(dimethylamino)ethane; DME = 1,2-dimethoxyethane; TMBD = 1,3-bis(dimethylamino)butane. [b] Cyclopentadienyl moiety. [c] C_4H_7: CH_2=CMeCH$_2$. [d] 340 K. [e] C_3H_5: CH_2=CHCH$_2$. [f] 213 K; diastereotopic splitting.

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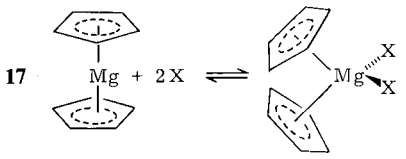
Kaiser-Wilhelm-Platz 1, D-4330 Mülheim a. d. Ruhr (FRG)
[+] NMR Spectroscopy.

Cp_2Mg **17** is a volatile compound that dissolves as a monomer in nonpolar solvents[5] and has a sandwich structure[6,7] which is isotypic with ferrocene and nickelocene. Despite numerous spectroscopic[8,9] and theoretical studies[7,8], the bonding relationships between Mg and Cp are the subject of controversy, and are described variously as more ionic or predominantly covalent. The ^{25}Mg-NMR parameters of Cp_2Mg suggest largely covalent character for the Mg–Cp bonds.



	X/X X
8	TMED
10	TMBD
11	THF
13	1,4-dioxane
14	DME
15	PMe_3
16	Et_2O

Because of the narrow line width of the Cp_2Mg signal, the complexation of Cp_2Mg with Lewis bases [eq. (a)] can be studied by ^{25}Mg-NMR spectroscopy. If Lewis bases are used as solvent, $\delta(^{25}Mg)$ increases with the complexation strength of the base: $(i\text{Pr})_2O \approx NEt_3 <$ anisole $< Et_2O < PMe_3 <$ 1,4-dioxane $<$ DME $<$ THF $<$ TMED.

Bis(2-methylallyl)magnesium **2** gives a signal at $\delta = 70.4$ ($W_{1/2}$ = 2000 Hz); Mg must therefore be preferentially η^1-bonded. A similar result is found for allylmagnesium bromide **5**. Previously, this could only be determined by time-consuming, isotopic-labeling techniques[10].

$$2\ RMgBr \rightleftharpoons R_2Mg + MgBr_2 \qquad (b)$$

The ^{25}Mg-NMR spectra of organomagnesium halides (Grignard compounds) are a function of the concentration and temperature. With EtMgBr, three species of the Schlenk equilibrium [eq. (b)] can be detected concurrently at 310 K (Fig. 2). The resonances for EtMgBr ($\delta = 62$) and $MgBr_2$ ($\delta = 12$) are resolved, and the broader signal of **1** is superposed by the signal group for EtMgBr. Direct evi-

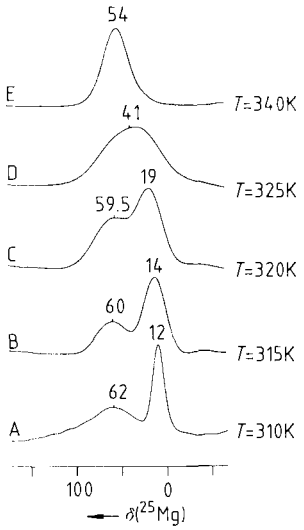


Fig. 2. ^{25}Mg-NMR spectra (24.49 MHz) of a 0.36 M solution of EtMgBr **4** in THF at various temperatures. At 310 K (A) the RMgX and MgX_2 species are directly identified in the presence of one another. The presence of R_2Mg follows from the coalescence behavior (B–D) and the high-temperature spectrum (E).

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dence for this is provided by the spectrum at 340 K. In accord with the shift in equilibrium in the direction of EtMgBr[3, 11], an average signal is found at $\delta = 54$. Since the equilibrium constant for the methyl compound MeMgBr $K \approx 30$[11] is larger than that for EtMgBr ($K = 5.1$)[3], **3** displays an averaged signal ($\delta = 67.8$), even at 300 K.

In the case of CpMgBr **9**, the ^{25}Mg signal is further removed from that of $MgBr_2$ and the line width is narrow enough to allow the Schlenk equilibrium to be studied quantitatively. Signals at $\delta = 16.3$ (1—2% **6**) and at $\delta = -26.8$ ($\approx$98% **9**) are observed for 1.38 M solutions of **9** in THF. The same chemical shifts and line widths are found when Cp_2Mg and $MgBr_2$ are mixed in the ratio 1 : 1 in THF. The signal intensities allow a value for the equilibrium constant to be estimated which is in good agreement with the value ($K = 10^5$)[12] obtained by extrapolation to 298 K.

In comparison with ^{1}H- and ^{13}C-NMR spectroscopy[10, 11, 13], ^{25}Mg-NMR spectroscopy has considerable advantages in the study of the Schlenk equilibria, since all three species can be recorded and identified directly from their typical chemical shifts. The large range of ^{25}Mg chemical shifts (ca. 200 ppm) permits unequivocal statements to be made about the bonding behavior such as, e.g., in **17** and **2**.

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1, 557-18-6; **2**, 69219-07-4; **3**, 75-16-1; **4**, 925-90-6; **5**, 1730-25-2; **6**, 7789-48-2; **7**, 14024-56-7; **8**, 90858-32-5; **9**, 34766-86-4; **12**, 90858-33-6; **13**, 90858-34-7; **14**, 90858-35-8; **17**, 1284-72-6.

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BOOK REVIEWS

Chemical and Biological Generation of Excited States. Edited by *W. Adam* and *G. Cilento*. Academic Press, New York 1982. xi, 388 pp., bound, $ 59.50.

The first seven chapters of this book give a detailed survey of the diverse aspects of the generation of excited states in chemical systems. Several sections are devoted to the chemistry of dioxetanes, covering the topics of synthesis, chemical characterization, activation (chemi- and photoenergization) and photophysical and photochemical transformations of the excited states. A critical and systematic survey of the techniques for their detection and calculation of excitation yields is presented. Without losing in originality, the chapter by *W. Adam* offers a useful and comprehensive introduction to the chemistry of dioxetanes, which enables the reader to go easily over other topics treated in this book. In addition, the activation parameters of over 50 well-studied 1,2-dioxetanes are summarized. In general, the chemical reports on these four-membered ring peroxides are sustained by common basic concepts that permit the reader to establish rapid comparisons, e.g., evaluation of dioxetane chemiluminescence in solution and in the gas phase. Solution-phase chemiluminescence resulting from electron-transfer reactions (electrochemiluminescence) is analyzed here on theoretical basis, and mechanistic implications for the production of the emitting state and experimental techniques are presented. These accounts on the chemistry of some excited states (mainly concerned with excited carbonyl compounds derived from dioxetane energization) give a synopsis of general and important concepts without being simplistic or falling into a long listing of observed details. They provide valuable up-to-date information for the chemist or biologist interested in the generation of excited states.

The final four chapters treat the generation of excited species in biological systems. The possible formation of singlet oxygen in some enzymatic reactions is discussed along with a short examination of the processes that can mimic singlet oxygen. At variance with the native chemiluminescent systems, the fluorophor-mediated chemiluminescence is also considered and the advantages of the use of such chemiluminigenic probes in the study of biological oxidations are listed. However, the disdavantages inherent in the addition of a foreign compound to a biological system are not taken into account. An outstanding contribution is the chapter on "Electronic Excitation in Dark Biological Processes". The author, *G. Cilento*, and his team have long been committed to a systematic study of the production of excited molecules which give the cell the potentialities of photochemistry in the absence of light. The section deals with the occurrence and generation of excited states and puts forward their role in biological processes. The possibility that one of the roles of peroxidases and some internal monooxygenases might be the formation of an electronic excited state product is exploited here on sound experimental grounds. No doubt the biologist could feel himself attracted to the discipline of "photobiochemistry in the dark" after these serious attempts for its characterization and definition.

In summary, the book gives an up-to-date account of the field and can be recommended to those interested in the occurrence of excited states in chemistry and biology.

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Vitamin B_{12}. Vol. 1: Chemistry; Vol. 2: Biochemistry and Medicine. Edited by *D. Dolphin*. Wiley Interscience, Chichester 1982. xiv, 671 pp., bound/xiv, 505 pp., bound, together £90.00.

This two-volume work, which is the most comprehensive up to now covering vitamin B_{12}, fulfills its claim to cover the chemistry, biochemistry and medicine of this group of compounds. It has been possible to recruit leading scientists for each of the topics to which a chapter is devoted.

Volume 1 with almost 600 pages of text is devoted to chemistry. A historical introduction *(Folkers)* and a summary of the nomenclature *(Cohn)* are followed by an extensive third chapter (84 p.) by *J. Pickworth-Glusker* devoted to the structures of corrinoids and containing a wealth of data not all of which had previously been published. The numerous tables and figures and the detailed discussion concerning structure-activity relationships make the few slight errors on p. 77 and 78 seem unimportant. The impressive advances made recently are described by *Battersby* and *McDonald* in a fascinating chapter on the biosynthesis of the corrin macrocycle. In chapter 5 there follows the biosynthesis of the cobalamine coenzyme (*Huennekens* et al.). The chapter on "The total synthesis of Vitamin B_{12}" by *Stevens* which is obligatory for any book on the subject presents this complex project, which has been the subject of previous reviews, in a very informative manner. The long needed summary of the rich chemistry of the corrin ligand by *Bonnett* is just as useful; here too, results are quoted that were until now only available in dissertations. Then follow two chapters concerning the synthesis *(K. L. Brown)* and reactivity *(Hogenkamp)* of organocobalt complexes. Chapters 10, 14, and 15 are particularly devoted to the central theme of coenzyme B_{12} chemistry, the reactivity of the Co–C bond. Chapter 10 by *Pratt*, engagedly and colorfully written, is detailed (68 p.) and contains an attempt to formulate a basic unified mechanistic view of the vitamin B_{12}-dependent isomerases that is not completely established and unchallenged in all aspects. Chapters by *Halpern* and by *Golding* close the first volume with discussions of the models and theories for coenzyme B_{12} catalyzed reactions. Chapters 11 (*Giannotti:* UV/VIS, CD, MCD), 12 (*Pilbrow:* ESR), and 13 (*Williams* et al.: NMR), which contain many data which had previously been scattered throughout the literature or were unpublished, are somewhat arbitrarily interposed between the contributions on the above range of topics.

The second, smaller volume covers biochemistry and medicine. Chapter 5 on metal-free corrinoids *(Koppenhagen)* is rather misplaced here and it would have been better to include it in the first volume. The "medical" chapters 1–4 *(Beck, Bradbeer, Nexø* and *Olesen)* which cover intrinsic factor, cobalamine transport and determination are easily readable and understandable for an organic chemist. A short informative chapter (15 p.) on methyl transfer reactions *(J. M. Wood)* is followed by one concerned with a discussion of acetate biosynthesis which goes beyond the bounds of corrin chemistry, by *Ljungdahl* and *H. G. Wood*. The second half of the volume contains seven detailed treatments of coenzyme B_{12}-catalyzed enzyme reactions. The common "design" (history, sources, isolation, measurement of the enzymes' activity; substrates and mechanism of the enzyme reaction) is enriched by the varied presentations of the authors *(Baker* and *Stadtman, Toraya* and *Fukui, Babior, Switzer, Taylor, Rétey, Blakley)*. The possibly unavoidable repetition of material already presented in chapters 9, 10, 14, and 15 of the first volume is not too disturbing.

Both volumes contain detailed subject and author indexes. The quality of the illustrations and the print is very high; the price is high but reasonable in comparison with similar works. These books can be highly recommended; not only are they a "must" for every scientist working in the vitamin B_{12} field but are also important, for example, for chemists dealing with organometallic compounds, bioorganic chemistry, or heterocyclic natural products. Apart from the well-done presentation of the "state of the art", the importance of this work lies in the fact that the many controversies and "unwritten chapters" in this long and intensively studied field are brought before our eyes.

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Ullmanns Encyklopädie der technischen Chemie. Edited by *E. Bartholomé, E. Biekert, H. Hellmann, H. Ley †, W. M. Weigert †*, and *E. Weise*. Verlag Chemie, Weinheim 1983. 4th Edition. Volume 23, Textilhilfsmittel bis Vulkanfiber. xv, 750 pp., bound, DM 545.00.

With the publication of the 23rd Volume of the 4th Edition of Ullmann[*] only one further volume and the general index are required to complete the series. This means that, on average, two volumes per year have been produced, a marvellous performance on the part of the editors and publishers, which is the more imposing if one takes the trouble to ascertain the number of authors involved in the production of a single volume. There were more than 80 for this volume.

Once again the subjects included in the volume are drawn from every area of industrial chemistry; that is, from inorganic chemistry: thallium, thorium, titanium, vanadium, and uranium together with their alloys and compounds, then the transuranic elements (excepting plutonium which is discussed in its own right in Volume 18) and some inorganic sulfur compounds (thiocyanic acid and thiourea); from organic chemistry come: vinyl compounds, toluene, toluidines and a range of organosulfur compounds (thiazoles, isothiazoles, benzothiazoles, organic thiocyanates and isocyanates, thioles, sulfides, polysulfides, thioglycolic acid, thiophene and benzothiophene); from application technology come: textile additives (102 p.), nonwovens, inks and other writing fluids, separating agents, drying agents, drying oils; from the area of raw materials come: composites, clay and clay minerals, pottery; then vitamins (108 p.), veterinary medicines, tri- and diarylmethane dyestuffs, peat. Then come two articles of particular topicality, namely thermo- and photoelectricity (28 p.) and the saccharification of starch and cellulose-containing materials (42 p.). Both these articles are concerned with topics touching on possible future forms of en-

[*] Cf. *Angew. Chem. Int. Ed. Engl. 23* (1984) 255.

ergy production, that is from solar cells and from natural polysaccharides (starch and cellulose). In both cases the decisive step is the utilization of solar energy, and Ullmann contains information for each topic concerning the present state of the art, possible developments and, above all, concerning the cost. Naturally the scientific basis is also outlined, i.e. the significant physical relationships in the case of solar cells and the chemistry and process technologies of the various methods and variants for the saccharification of starches and cellulose. A further example of the topicality of the contents is the article on thallium, where the problem of the environmental dangers of thallium emissions from industrial plants is discussed on the basis of recent knowledge in the section on toxicology.

The volume naturally contains much more that is worthy of note alongside such particularly topical information. Apart from the descriptions of manufacturing processes and possibilities for application and a great deal of statistical information it is the clear and concise information concerning the chemical and physical properties of individual compounds that make this volume, like its predecessors, of interest to chemists. The production is, as ever, excellent (readable type, clear and easily understandable graphics, perfect printing), so that it is a joy to pick up the volume and leaf through it.

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Technische Chemie I. Grundverfahren. By *W. Brötz* and *A. Schönbuchen.* Verlag Chemie, Weinheim 1983. xvi, 338 pp., bound, DM 68.00.

The first volume of this two-volume work presents the general basic principles of chemical engineering. Based on the "Lehrprofil Technische Chemie" of the Dechema training committee of May 1981 this clearly planned text book is particularly designed for comprehensibility. The authors present a survey of the three main branches of chemical engineering that are usually covered in technical universities by mechanical process technology, thermal process technology and chemical reaction technology.

In advance of the presentation of the unit processes of these three branches the first part of the book delivers the necessary basic knowledge from physics and physical chemistry, fluid dynamics and thermodynamics of material and thermal transport. A large number of tabular presentations ranging from units of measurement via dimensionless numbers, resistance values, diffusion and material transfer coefficients, to aids for the calculation of heat transfer and heat diffusion coefficients help give this volume the character of a reference book.

The section on mechanical unit processes includes all those unit operations which proceed without material alteration (chemical reaction). With the aid of numerous diagrams and cross-sectional drawings of apparatus, detailed accounts are given on storage, transport, the mixing of liquids, gases and bulk solids, the separation of disperse systems (solid/liquid, solid/gaseous) and the classification, sorting and comminution of bulk solids. Under the major headings of bulk solid/fluid and fluid/fluid contact,the type and layout of apparatus are introduced that find application in thermal and reaction engineering processes. Thus, the most important variables affecting the design of solid beds, fluidized beds, stirrers, and rotating drums are given, together with their main fields of application. The same applies to fluid-fluid contacting equipment such as fluid film contactors, packed columns, spray towers, bubble columns and plate columns.

The section on thermal processes first gives a detailed treatment of the problems of heating and cooling. The section dealing with the production of process heat and cooling and thermal transport media, is followed by a large section on the actual equipment used in heat exchange and its construction. The following sections covering unit operations, distillation and rectification, absorption, extraction, adsorption, drying, and crystallization are laid out in a way that the presentation of the thermodynamic basis of the operation is followed by details of the construction of the plant; this makes fundamental information easily available. The presentation of drying and, in particular, the application of the Mollier diagram is particularly thorough.

The unit processes in reaction engineering are subdivided into thermal, electro-, photo-, and biochemical reactions, the largest amount of space being dedicated to thermal reactions. The concept of the thermal reaction utilized here is justified in that the resistance to reaction is overcome by the choice of the temperature of the reacting mass. A discription of the various types of reactors is then followed by a discussion of the methods of calculation and the fundamental behavior of stirred reactors (continuous and batch) and tube reactors in terms of a simple first order reaction; this is followed by a clear comparison of productivities. Residence time distributions and the techniques for their measurement are then discussed, as are also complex reactions. The influence of thermal and material transport on the course of the reaction and the consequences for the choice and dimensioning of the reactor are presented in a very easily understandable form. The electro-, photo-, and biochemical reactions are outlined in a very few pages.

This book is also likely to be of interest to those chemists employed in industry who require an optimal introduction to the unit processes of chemical engineering. Used as a textbook the work can provide the new student of chemical engineering and process technology with an easily understandable survey of the major aspects of his course. The copious references to the more advanced literature are invaluable for more detailed study.

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Isotopeneffekte bei chemischen Reaktionen. By *Alfred V. Willi,* Georg Thieme Verlag, Stuttgart 1983. x, 180 pp., bound, DM 80.00.

Because several exhaustive books are already available covering this topic the particular aim of the author has been to close a gap in the German-language chemical literature with a short treatment.

Thus the reader proceeds from the 1st Chapter "The theory of isotope effects in chemical reactions" (p. 5—29) to the 2nd Chapter "Isotope effects in chemical equilibria" (p. 32—61). The third chapter deals with the topic "Kinetic isotope effects and mechanism" (p. 62—135), while the title of the last chapter is "Kinetic isotope effects and the transition state" (p. 139—159). The text is completed by 443 literature references and an index (5 1/2 pages) that is almost too short.

There is no doubt that the book fulfills its purpose: Anyone dealing with isotope effects for the first time can find

all the significant aspects mentioned within the compass of not too many pages and also a rapid entry into the original literature. Its limitation consists of the lack of an adequate discussion of the isotopic perturbation method, a nuclear magnetic resonance technique by *M. Saunders* et al. (*J. Am. Chem. Soc. 93* (1971) 2558; *ibid. 105* (1983) 3571, and references cited therein) which, above all, allows a decision as to whether rapidly equilibrating molecules (ions) or a symmetrical delocalized molecule (ion) is being studied.

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Chirurgische Onkologie. Edited by *H. Denck* and *K. Karrer*. Edition medizin, Weinheim 1983. xvi, 707 pp., bound, DM 278.00.—ISBN 3-527-15008-0

Neue Aspekte der Energieforschungspolitik. Ausgewählte Reden und Mitteilungen aus dem Bundesministerium für Forschung und Technologie. Issued by the Bundesminister für Forschung und Technologie. Verlag TÜV Rheinland, Köln 1983. 160 pp., boards, DM 7.00.—

Max-Planck-Gesellschaft—Jahrbuch 1983. Verlag Vandenhoek und Ruprecht, Göttingen 1983. 844 pp., bound, DM 72.00.—

Raffinationsverfahren in der Metallurgie. A publication of the GDMB Gesellschaft Deutscher Metallhütten- und Bergleute. Verlag Chemie, Weinheim 1983. viii, 302 pp., stitched, DM 120.00.—ISBN 3-527-26127-3

Chemie für Ökologen. By *R. K. M. Hay*. Revised by *A. Hüttermann*. Ferdinand Enke Verlag, Stuttgart 1983. 272 pp., stitched, DM 34.00.—ISBN 3-432-93421-1

Korrosionskunde im Experiment. Untersuchungsverfahren—Meßtechnik—Aussagen. Erweiterte Fassung eines Experimentalkurses der DECHEMA. By *E. Heitz, R. Henkhaus,* and *A. Rahmel*. Verlag Chemie, Weinheim 1983. xv, 316 pp., stitched, DM 54.00.—ISBN 3-527-26070-6

Chirurgie der Leber. Edited by *R. Häring*. Edition medizin, Weinheim 1983. xxi, 464 pp., stitched, DM 180.00.—ISBN 3-527-15095-1

Pollution: Causes, Effects and Control. Edited by *R. M. Harrison*. The Royal Society of Chemistry, London 1983. 322 pp., stitched, £ 12.00 (Preisnachlaß für Mitglieder der Roxal Society of Chemistry).—ISBN 0-85186-875-4

Nouvelles Recherches dans le Domaine des Composés Macromoléculaires. By *E. Ceausescu*. Pergamon Press, Oxford 1984. ix, 451 pp., bound, £ 45.00.—ISBN 0-08-030725-6

Specialist Periodical Reports: Organophosphorus Chemistry. Vol. 14. A Review of the Literature published between July 1981 and June 1982. Edited by *D. W. Hutchinson* and *J. A. Miller*. The Royal Society of Chemistry, London 1983. xiv, 347 pp., bound, £ 56.00 (price reduction for members of the Royal Society of Chemistry), total price for Vol. 1—14 £ 256.00.—ISBN 0-85186-126-1

Specialist Periodical Reports: Catalysis. Vol. 6. A review of the Recent Literature published up to mid-1982. Edited by *G. C. Bond* and *G. Webb*. The Royal Society of Chemistry, London 1983. xii, 234 pp., bound, £ 43.00 (price reduction for members of the Royal Society of Chemistry), total price for Vol. 1—6: £ 143.50.—ISBN 0-85186-574-7

Special Publication No. 45: Chemicals in the Oil Industry. Proceedings of a Symposium Organized by the North West Region of the Industrial Division of the Royal Society of Chemistry, University of Manchester, March 22—23, 1983. Edited by *P. H. Ogden*. The Royal Society of Chemistry, London 1983. 217 pp., stitched, £ 12.00 (reduced price for members of the Royal Society of Chemistry).—ISBN 0-85186-885-1

Einführung in die Photochemie. 2nd newly revised edition. Edited by *H. G. O. Becker*. Georg Thieme Verlag, Stuttgart 1983. 511 pp., bound, DM 70.00.—ISBN 3-13-633702-6

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Cobalt-Mediated [2+2+2]-Cycloadditions: A Maturing Synthetic Strategy

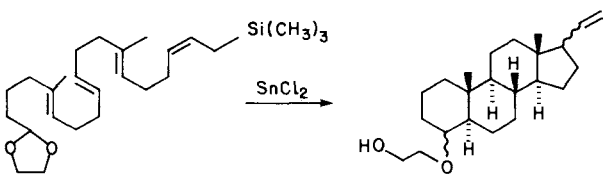
New Synthetic Methods (43)

By K. Peter C. Vollhardt*

Dicarbonyl(η^5-cyclopentadienyl)cobalt functions as a matrix on which a variety of unsaturated organic substrates undergo mutual bond formation. In this way α,ω-diynes cocyclize with monoalkynes to give annelated benzenes, while *o*-diethynylbenzenes furnish biphenylenes, and α,ω-enynes lead to the formation of complexed bi- and tricyclic dienes. Nitriles cocyclize with two alkynyl groups to give pyridines and other heterocycles, isocyanates allow access to annelated 2-pyridones, and incorporation of carbon monoxide provides complexed cyclopentadienones. In many cases remarkable chemo-, regio-, and stereoselectivity are observed, partially facilitated by use of the trimethylsilyl substituent as a controlling group. The scope and level of maturity of the method are demonstrated by the synthesis of a series of hitherto inaccessible, novel, and theoretically interesting molecules, and by its utilization in several unique approaches to a variety of natural products, e.g. protoberberines, steroids, vitamin B_6, and camptothecin.

1. Introduction

The discovery and control of new bond formations are two of the primary tasks of the synthetic organic chemist. The arsenal of current synthetic methods has already allowed the construction of even the most complex natural products and most remarkable, "unnatural" molecular assemblies. Nevertheless, despite these advances, there remains much room for improving and particularly simplifying synthetic strategies. This can be done by either cleverly manipulating existing methodology or, probably more successfully, by finding new methods through which simple materials are converted into structures of greater complexity. In this connection we deem it especially important to design new reactions in which a maximum change of topological complexity[1] can be effected with the highest degree of efficiency and selectivity. Many cycloaddition reactions fall into this category, because at least two bonds may be formed in one step while steric and electronic factors reduce the number of options available to the substrates en route to the products. A striking example is the cyclization reaction of *Johnson* et al.[2] in which a stereospecifically constructed polyene undergoes acid-catalyzed multiple ring closure to the steroid nucleus (Scheme 1).



Scheme 1. Polyene cyclization according to *Johnson* et al. [2].

Perhaps the most widely used cycloaddition reactions are the Diels-Alder cyclizations (Scheme 2) and their various modifications[3]. Typically, six-membered rings are generated by two CC bond formations with the potential

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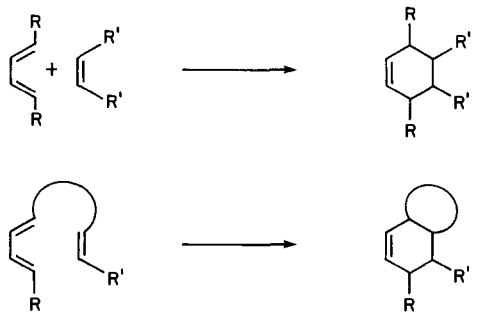
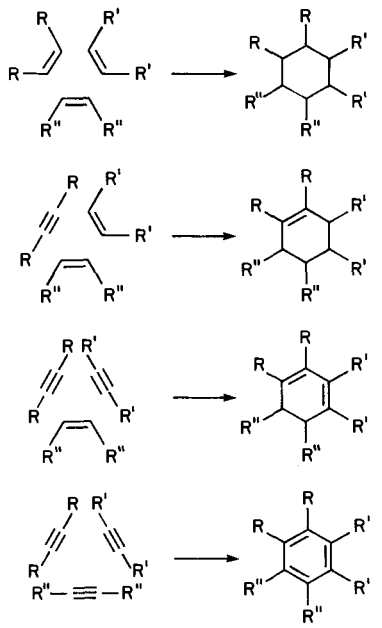
to construct four chiral centers. More complex topological changes may ensue on application of its intramolecular version (Scheme 2)[4]. The power of this method lies in its extraordinary specificity: it is chemoselective, in other words the dienophile prefers to react with the diene, and neither of the starting materials react competitively with themselves; it is regioselective, unsymmetrical dienes choosing only one sense of cycloaddition to unsymmetrical dienophiles; and it is stereoselective, mostly following the *endo*-rule.



Scheme 2. Inter- and intramolecular Diels-Alder reactions.

A simple analysis shows that a potentially more powerful strategy would be one based upon the [2+2+2]-cycloaddition of three unsaturated moieties (Scheme 3). Now three new bonds would be constructed in one step, constituting a considerably larger change in molecular complexity, and up to six chiral centers could be generated from completely achiral starting materials.



Scheme 3. Prototypical [2+2+2]-cycloadditions.

Employment of varying proportions of cycloaddends containing double and triple bonds would provide access to six-membered, partially or completely unsaturated rings. As in the Diels-Alder reaction, one could also envisage the use of heteroatomic units furnishing various heterocyclic systems[5] and a plethora of partially or completely intramolecular versions.

It is surprising that, although symmetry-allowed[6], and in most cases strongly exothermic[7], there is a paucity of examples of purely thermal [2+2+2]-cycloadditions. It is possible that entropic and, in some cases, enthalpic[8] activation energy contributions account for the relative rarity of these transformations. This report will describe how the use of a transition metal, particularly cobalt in the form of the dicarbonyl(η^5-cyclopentadienyl) derivative $CpCo(CO)_2$ as a catalyst or reagent may lead to the successful execution of a variety of [2+2+2]-cycloadditions of the type depicted in Scheme 3. The many previously unattainable molecules generated in this way have been used as starting materials for the preparation of several unnatural and natural products of theoretical and/or medicinal-synthetic interest.

2. α,ω-Diyne Cyclizations in the Preparation of Annelated Benzene Derivatives: Control of the Substitution Pattern

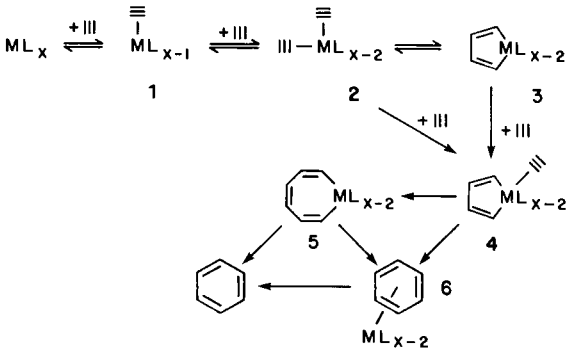
2.1. Background

Berthelot reported in 1866 on the thermal cyclization of acetylene to benzene[10]. High temperatures (ca. 400 °C) are required and a mixture of products is formed[11]. In 1949, *Reppe* et al. described the first transition metal catalyzed version of this transformation, in which nickel was employed, and which under certain conditions leads to the predominant formation of cyclooctatetraene[12]. Subsequently, it was found that a large number of transition metal systems catalyze the cyclotrimerization of substituted, frequently functionalized alkynes to benzene derivatives[13]. At the outset of the work described in this account, comparatively little was known about the utilization of these reactions in organic synthesis, particularly when employing oligoynes, even though such reactions would hold considerable potential in complex molecule construction. The validity of this premise was indeed demonstrated earlier when it was shown that a variety of oligocycles were obtainable by cyclization of α,ω-diynes[14]. Furthermore, in a series of over 40 papers, *Müller* et al. showed that stoichiometric amounts of rhodium complexes could be used in the "diyne reaction" to generate a multitude of rhodacycles capable of varied reactivity to furnish quinones, carbocycles, and heterocycles[15]. Although the method has its limitations with respect to scope, generality, and expense, it clearly pointed out some of the possibilities in store. Very recently, other groups have become interested in this problem[16].

2.2. General Mechanistic Considerations

Based on the results of several investigators, the general Scheme 4 may be formulated for the mechanism of cyclotrimerization of acetylene to benzene catalyzed by low valent transition metal complexes[17]. Initially, one and then two alkyne moieties sequentially displace two ligands on

the metal to form alkyne complexes **1** and **2**. Oxidative coupling may occur to give the coordinatively unsaturated metallacyclopentadiene **3**, in which the metal has adopted a formal oxidation state two units higher than in its precursor **2**. This change appears to facilitate chemoselectivity in

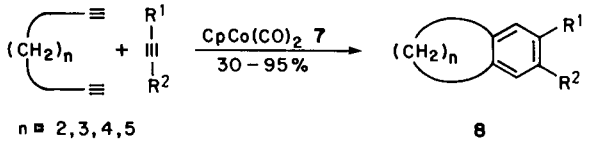


Scheme 4. Mechanism of cyclotrimerization of acetylene.

certain cases. Complex **3** may then coordinate a third molecule of alkyne to give **4**. On the other hand, calculations show that the direct conversion of **2** into **4** should be kinetically more advantageous[18], since coordinative unsaturation is avoided. Species **4** appear to be very reactive, since, in contrast to **2**, **3**, **5**, and **6**, derivatives of which have been characterized, it has so far eluded isolation. This is unfortunate, because its preparation could provide crucial information with respect to the next step in the catalytic cycle: either an alkyne-insertion to form the metallacycloheptatriene **5** or a Diels-Alder type addition to furnish the benzene complex **6**. Precedence exists for the conversion of either species into the free arene[17], and perhaps both options are viable.

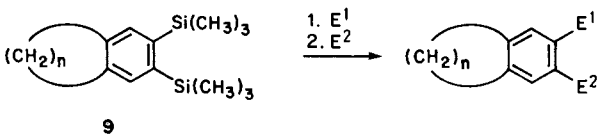
2.3. Cobalt-Catalyzed Cocyclizations to Benzocycloalkenes

Approximately 10 years ago, it was found that $CpCo(CO)_2$ **7** catalyzes a variety of [2+2+2]-cycloadditions involving α,ω-diynes to give annelated benzenes **8** as shown in Scheme 5[19]. The reaction works best for n=3 and 4 and tolerates a wide variety of substituents, such as R=H, alkyl, aryl, vinyl, CO_2R', CH_2OH, CH_2OR', COR', C=NOR', NR'_2, SR', and $Si(CH_3)_3$. In some cases there is a problem of chemoselectivity in as much as alkynes of comparable bulk or electronic make-up tend to undergo random cyclizations. The presence of substituents at the terminal position of the diyne may also lead to diminished yields when bulky groups such as $Si(CH_3)_3$ are involved[20]. Although the reaction is poor for the preparation of benzocycloheptenes **8**, n=5, it is capable of generating strained four-membered rings, thus providing a fairly general synthetic entry to the 1,2-dihydrocyclobutabenzenes (benzocyclobutenes) **8**, n=2, which are useful synthetic intermediates (see Section 3.1). Functional groups such as NO_2, alkyl halides, and reactive vinyl and aryl halides are detrimental to the catalyst, presumably due to facile oxidative addition processes[17]. On the other hand, chlorophenylalkynes are readily cyclized according to Scheme 5[20].

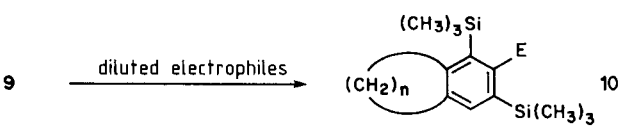


Scheme 5. $CpCo(CO)_2$-catalyzed cocyclotrimerization of α,ω-diynes with alkynes.

In order to circumvent the aforementioned problems of chemoselectivity, bulky alkynes may be employed, particularly trimethylsilylalkynes which are too sterically hindered to autocyclize but not so encumbered not to cocyclize. Their application (usually in excess) frequently results in excellent yields of the corresponding annelated arenes[19–21]. The trimethylsilyl group in the products functions as an excellent leaving group in electrophilic aromatic substitution reactions[22]. This is particularly advantageous when employing bis(trimethylsilyl)acetylene (BTMSA) in the cyclization reaction, since the resulting *o*-bis(trimethylsilyl)benzene derivatives **9** can be substituted selectively and in high yield in a step-wise manner (Scheme 6)[19,20]. Even in the case of deuteriodesilylation the first silyl group is more reactive than the second by a factor of about 40[19c]. Another interesting feature of compounds **9** is their ability to rearrange to the *m*-bis(trimethylsilyl) derivatives **10** when exposed to dilute electrophiles (Scheme 7)[19c,23]. This phenomenon appears to be caused by the slow rate of desilylation of the cationic intermediate formed during electrophilic aromatic substitution relative to 1,2-silyl migration, relieving steric strain, followed by rapid deprotonation.

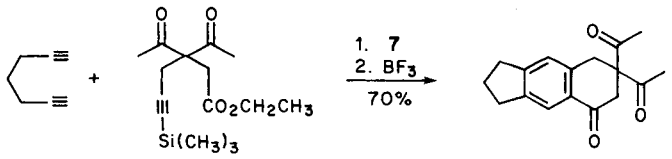


Scheme 6. Selective electrophilic aromatic substitution of *o*-bis(trimethylsilyl)arenes.



Scheme 7. Rearrangement of *o*-bis(trimethylsilyl)arenes (E=H, Br).

An example of the use of the cobalt-catalyzed cocyclization reaction, incorporating a silicon-directed intramolecular regioselective Friedel-Crafts acylation[21], is illustrated for the synthesis of a linear annelated tricycle in Scheme 8.



Scheme 8. Formation of a linear annelated tricycle by $CpCo(CO)_2$-catalyzed cyclization and silicon-directed intramolecular Friedel-Crafts acylation.

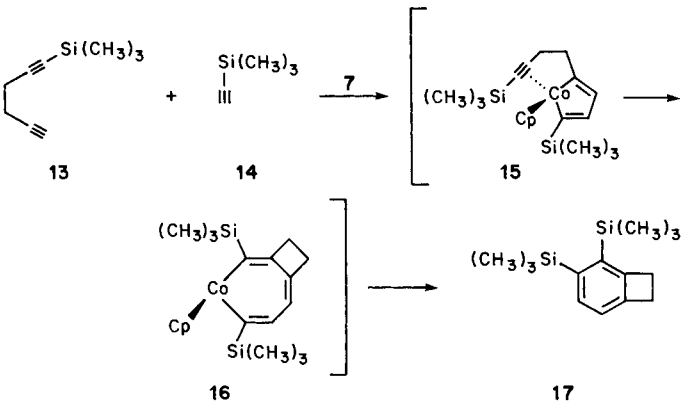
2.4. Specific Mechanistic Considerations

If we recall the discussion in Section 2.2 and apply its conclusions to the case of $CpCo(CO)_2$, there are two cobaltacyclopentadiene intermediates of the type **4** to be considered, namely **11** and **12** (Scheme 9). The mechanism of the reaction of $CpCo(CO)_2$ with alkynes to give cobaltacyclopentadienes and ultimately benzene derivatives has been well investigated[17,24,25]. Intermediates such as those of the type **11** (but not **12**) have been isolated[26], except for n=2, although a related iron compound is known[27]. Cyclobutadiene complexes derived from both **11** and **12** are obtained as by-products in catalytic reactions employing α,ω-diynes[19,20,28] and are responsible for some of the catalyst depletion, since they appear to be unsuitable as precursors for any catalytic intermediates[29,30]. On the basis of previous findings, neither of the two possible intermediates **11** or **12** can be ruled out; indeed, either one or both may be formed depending on the reaction conditions and substrate structures.

Scheme 9. Proposed cobaltacyclopentadiene intermediates in the cocyclization of α,ω-diynes with alkynes.

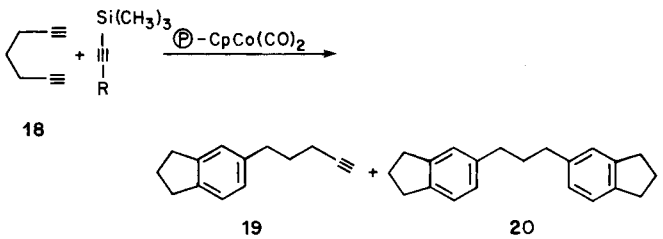
The structure of **12**, with the alkynyl group in the α-position, is in accord with expectations based on steric arguments[24a]. These arguments also predict that R^1 should be larger than R^2. Electronic factors, in particular the polarization of the alkyne π* orbital, are, however, thought to favor the preferential emergence of alkyl substituents in the β-position, whereas the trimethylsilyl group should, according to both theories, occupy the α-position[31]. The inconsistency of some of the predictions with the experimental results[24a] may simply be due to thermodynamic factors. Since the oxidative coupling of two complexed alkynes to a cobaltacyclopentadiene proceeds endothermically (by an estimated 14 kcal/mol), this step may well be reversible; hence, the observed regioselectivity of the cyclization may not in any way reflect the initial course of the reaction. In the specific case of systems of the type **12**, it may also be that additional involvement of the appendant alkyne group in the transition state for oxidative coupling (modelled by **2**→**4** in Scheme 4) controls the outcome of the process.

The trimethylsilyl group, which is used extensively for controlling the chemo- and regioselectivity, has a pronounced tendency to α-selectivity in the metallacycle (vide infra), as can be concluded from product isolation studies. An example of how this effect may be synthetically exploited in the formation of **17** as the sole isomer on cocyclization of 1-trimethylsilyl-1,5-hexadiyne **13** and trimethylsilylacetylene **14** is shown in Scheme 10[19c]. On steric grounds the kinetically favored metallacycle is expected to be **15**, which, after insertion of the complexed alkyne to give **16**, can only lead to **17**.



Scheme 10. Exclusive formation of the regioisomer **17** in the cyclization of **13** with **14**.

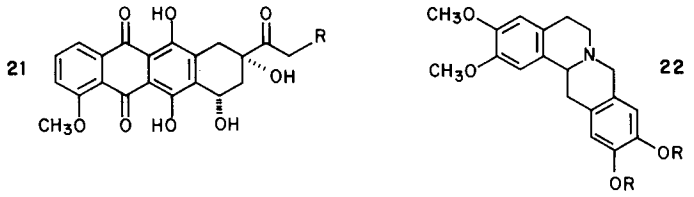
A mechanistically curious and synthetically unexploited result was obtained when attempts were made to catalyze cocyclizations of the type shown in Scheme 5 with polystyrene-supported $CpCo(CO)_2$[32] (Scheme 11). The monosubstituted acetylenes were not incorporated into the aromatic products, and only diyne dimers, such as **19** (major product), and trimers, such as **20**, were isolated. Since homogeneous $CpCo(CO)_2$ converts **18** exclusively into **20**, indicating that the catalyst is transferred intramolecularly from the benzene ring in **19** to the appendant alkyne unit, which is next to be cyclized, and since $CpCo(CO)_2$ also cocyclizes trimethylsilylalkynes, the polystyrene-supported or similar catalysts may offer an opportunity for interesting shape-selectivity in some of these transformations.



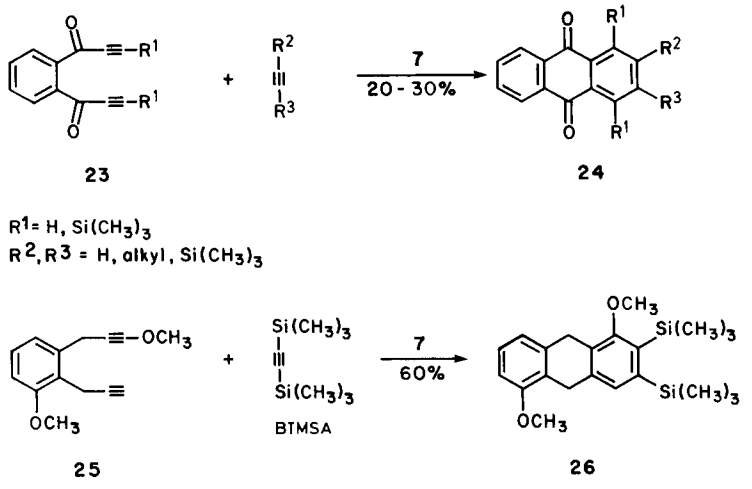
Scheme 11. Catalytic cyclization of 1,6-heptadiyne by polystyrene-supported $CpCo(CO)_2$. Ⓟ = polystyrene.

2.5. Synthetic Applications: Anthracycline Antibiotics and Protoberberine Alkaloids

The $CpCo(CO)_2$-catalyzed [2+2+2]-cycloaddition of three alkyne units could in principle be applied to the total synthesis of a variety of natural products containing annelated benzene rings. Two target molecules which require 1,7-octadiyne structures as cooligomerization precursors are the antitumor anthracycline aglycones **21**[33] and the protoberberine alkaloids **22**[34]. Both systems have already been synthesized via a multitude of approaches, none, however, involving the retrosynthetic disconnection made possible by the "cobalt-way". Two strategies are currently being employed en route to anthraquinone type antibiotics

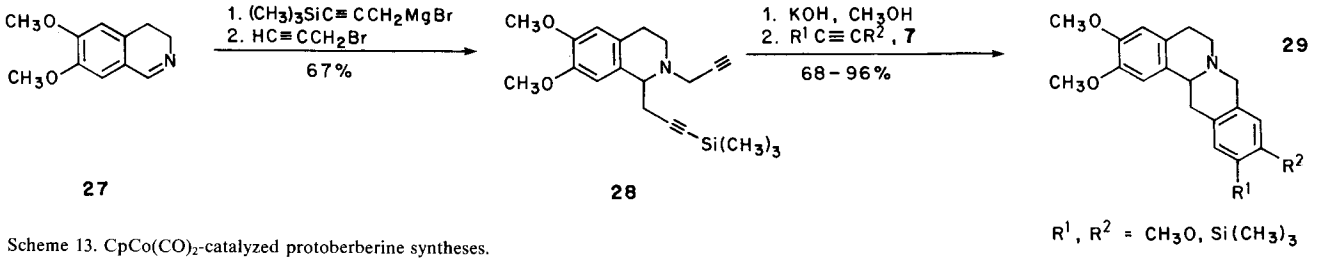


(Scheme 12), one involving the cyclization of aromatic bis(alkynylketones) **23** to furnish directly the desired framework **24**, albeit in only moderate yields[19c], the other utilizing dipropargylbenzenes of the type **25** to assemble initially a dihydroanthracene nucleus as in **26**[35].



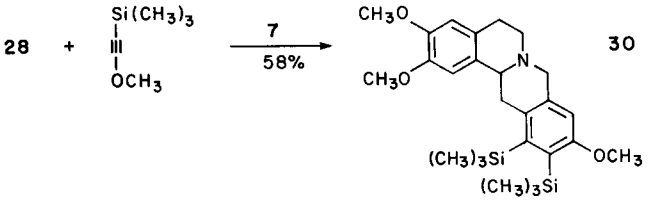
Scheme 12. Two cyclization strategies for the preparation of anthraquinones.

The protoberberines **29** are readily accessible by the sequence of reactions shown in Scheme 13[36]. For example, **29**, $R^1=R^2=Si(CH_3)_3$, is formed in 96% isolated yield by cocyclization of **28** with bis(trimethylsilyl)aceylene (BTMSA). Unfortunately, but perhaps not unexpectedly, unsymmetrical alkynes [$R^1=CH_3O$, $R^2=Si(CH_3)_3$] cyclize non-regioselectively. However, such selectivity is attainable starting from **28**, again the sterically more demanding



Scheme 13. $CpCo(CO)_2$-catalyzed protoberberine syntheses.

arene, e.g. **30**, being generated exclusively (Scheme 14)[36]. Finally, the trimethylsilyl substituents in the compounds **24**, **26**, **29**, and **30** can function as leaving groups in electrophilic aromatic substitution reactions.

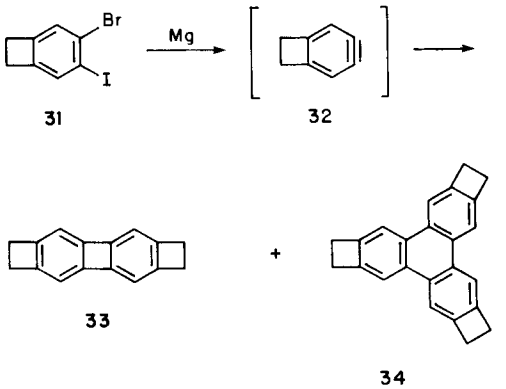


Scheme 14. Regioselective protoberberine synthesis.

3. Theoretically Interesting Molecules

3.1. 1,2-Dihydrocyclobutabenzenes (Benzocyclobutenes)

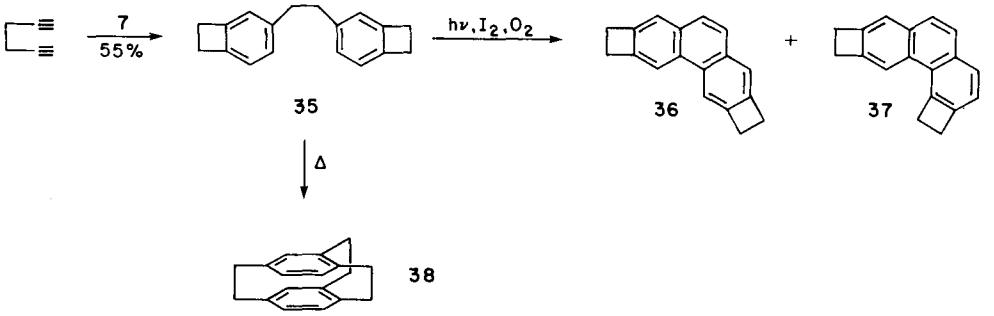
The ready access to functionalized 1,2-dihydrocyclobutabenzenes according to Scheme 5 has enabled their use in the construction of a host of theoretically interesting, strained ring activated, benzenoid hydrocarbons[37]. Thus, 4-bromo-5-iodo-1,2-dihydrocyclobutabenzene **31** (Scheme 15) functions as a precursor of **33**[38] and **34**[39] *via* the intermediacy of 1,2-dihydro-4,5-didehydrocyclobutabenzene



Scheme 15. Generation and oligomerization of 1,2-dihydro-4,5-didehydrocyclobutabenzene.

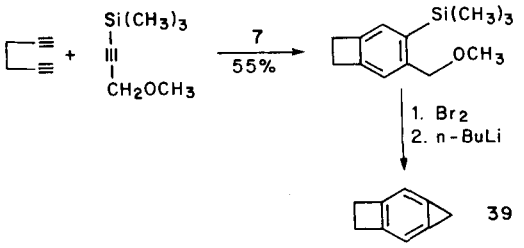
32. The activating effect of the four-membered ring is reflected in the physical and chemical properties of the products. Thus, e.g., both **33** and **34** are rapidly hydrogenated over platinum at ambient pressures. In a similar sequence, compound **17** afforded 1,2-dihydro-3,4-didehydrocyclobutabenzene, predicted by bond fixation arguments to be more reactive than **32**[40].

Hydrocarbon **35**, readily prepared in one step by trimerization of 1,5-hexadiyne, undergoes oxidative photocyclization to give the two isomeric dicyclobutaphenanthrenes **36** and **37** (Scheme 16)[41]. In contrast to **36** and phenanthrene itself, the more reactive **37** is mutagenic in the Ames test, and thus constitutes the first substance in which such physiological activity is increased by ring strain. Flash vacuum pyrolysis[42] of **35** results[43] in diastereoselective cycloaddition to give cyclophane **38**; the conceivable alternative isomer (±)-[2.2.2](1,2,4)(1,2,5)cyclophane[44] could not be detected. This preparation of **38** is clearly the method of choice[45].



Scheme 16. Synthesis of strained ring systems from **35**.

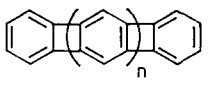
The currently most severely strained simple annelated benzene derivative is probably[46] **39**, which can be prepared rapidly as in Scheme 17[47]. This sequence is comparable in effectiveness with an alternative route[48] because of its speed, even though the last cyclization step is poor (≈5% yield).



Scheme 17. $CpCo(CO)_2$-catalyzed synthesis of 3,4-dihydro-1*H*-cyclobuta[*a*]cyclopropa[*d*]benzene **39**.

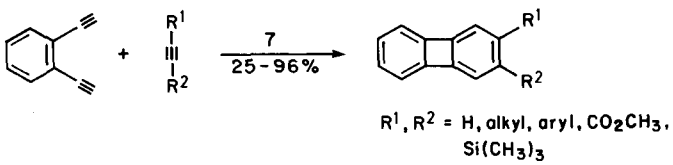
3.2. Multiphenylenes and Related Hydrocarbons

Cobalt-catalysis has opened up an iterative synthetic approach to the preparation of a novel series of cyclobutadienoid[49] aromatic polycyclic hydrocarbons **40**, termed multiphenylenes (biphenylene, terphenylene, etc.), in analogy to the multiphenyls (biphenyl, terphenyl, etc.). Curiously, the series is alternating with respect to the π-electron count of the individual members between formally antiaromatic and formally aromatic. Theory predicts[50] a rapidly narrowing HOMO-LUMO gap with increasing n. Therefore, these compounds might have potential as novel materials with conductive behavior[51].

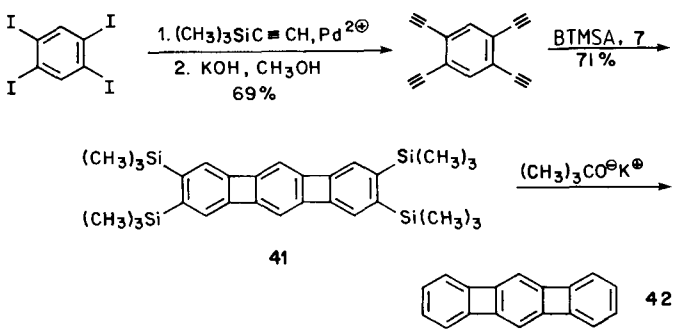


40

The synthetic strategy is based on the palladium-catalyzed ethynylation of halobenzenes[52], on the cobalt-catalyzed cotrimerization of *o*-diethynylarenes with alkynes to give biphenylenes (Scheme 18)[53], and on the ability of the trimethylsilyl group to function as a masked halogen. Scheme 19 depicts the rapid construction of terphenylene **42**, the first new member in the series[54].



Scheme 18. A $CpCo(CO)_2$-catalyzed biphenylene synthesis.

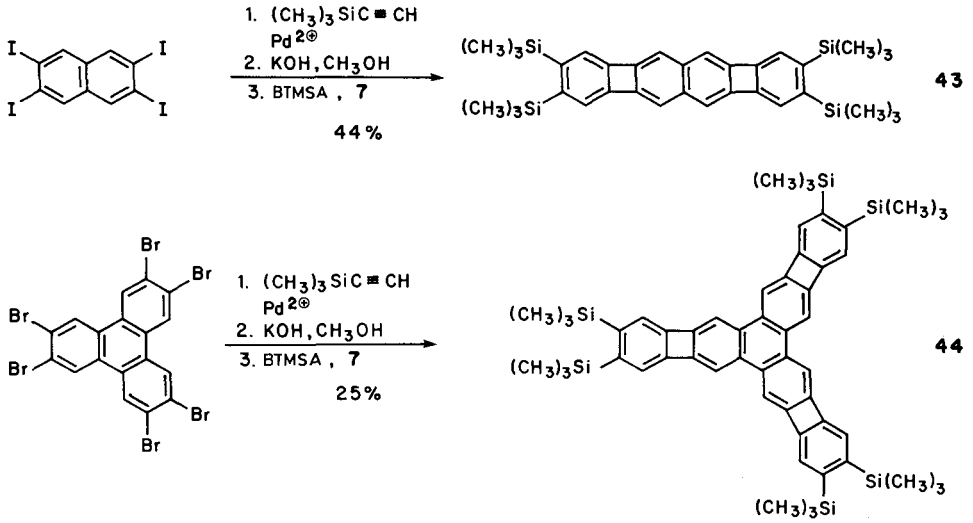


Scheme 19. Synthesis of terphenylene.

The cyclization of 1,2,4,5-tetraethynylbenzene to **41** is the first reaction to form four rings in one step. Even though terphenylene has 18 π-electrons, the system does not behave like an [18]annulene, either physically or chem-

ically. Although the two outer benzene rings show considerably more bond alternation than the central ring, as revealed by an X-ray crystallographic investigation[55], it is the central "cyclohexatriene" which exhibits unusual reactivity: it hydrogenates (all-*cis*) faster than a normal alkene and it adds both electrophiles and alkyllithium reagents. The dianion is surprisingly diatropic[55], suggesting that the system avoids antiaromatic circuits[56].

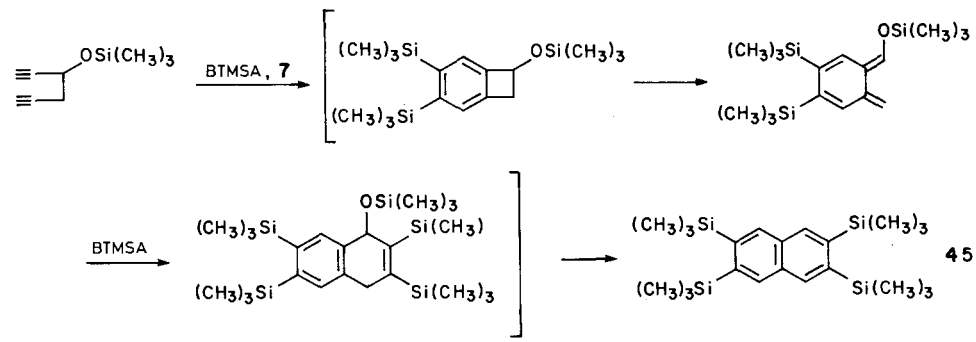
cocyclization of 1,5-hexadiynes with alkynes can be utilized in the construction of more complex assemblies by exploiting their ability to ring-open thermally to the reactive *o*-quinodimethanes, which subsequently undergo Diels-Alder cycloadditions[19,20]. A particularly interesting example is shown in Scheme 21; five of the carbon-carbon bonds of the naphthalene **45** are made in one step[58]. The product **45** not only enables a facile synthesis of otherwise



Scheme 20. A novel synthesis of hydrocarbons containing biphenylene units.

The methodology for the preparation of **42** is of general utility, as shown by the additional examples in Scheme 20[57]. Its effectiveness becomes apparent when one reflects that eleven (!) of the bonds present in **43** are formed by cobalt catalysis; the precursor of **43**, 2,3,6,7-tetraiodonaphthalene, is prepared by iodination of **45** (Scheme 21). The cyclization furnishing **44** constructs a record number of, e.g., six rings in one step.

inaccessible 2,3,6,7-tetrasubstituted naphthalene derivatives[57,59], but its preparation also demonstrates the feasi-

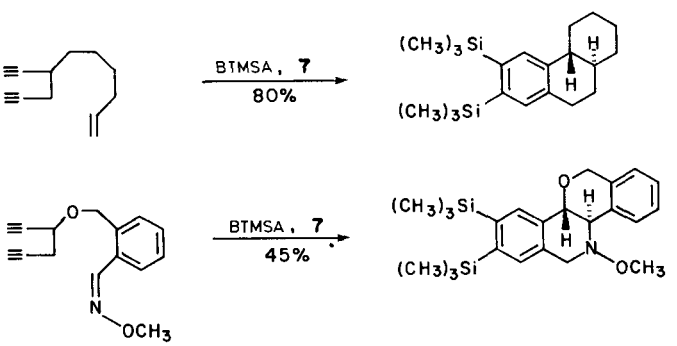


Scheme 21. A one-pot synthesis of naphthalenes according to the "tandem principle".

4. Coupling of Alkyne Cooligomerizations and *o*-Quinodimethane Cycloadditions: The "Tandem Principle"

4.1. A One-Pot Synthesis of Polycycles

Aside from their use in the synthesis of strained ring systems, the 1,2-dihydrocyclobutabenzenes generated by the



Scheme 22. One-pot syntheses of polycyclic compounds according to the "tandem principle".

bility of executing tandem cyclization-cycloaddition reactions. When the latter are carried out intramolecularly[58b,60], polycyclic systems are assembled chemo-, regio- and stereoselectively with remarkable ease. Two of several examples are shown in Scheme 22. The observed stereoselectivity appears to be controlled by the intermediacy of an *o*-quinodimethane formed by conrotatory outward opening of the initially generated 1,2-dihydrocyclobutabenzene, followed by an *exo*-Diels-Alder closure[58b,60]. Control experiments demonstrate that the metal is not involved in the latter.

4.2. The Cobalt-Way to (±)-Estrone: the D→ABCD Approach

Based on the above model systems, a $CpCo(CO)_2$-catalyzed steroid synthesis may be designed as in Scheme 23[61], in which in the crucial step the ABC portion of the steroid nucleus is fused onto the D-ring already present. The salient features of this synthesis are:

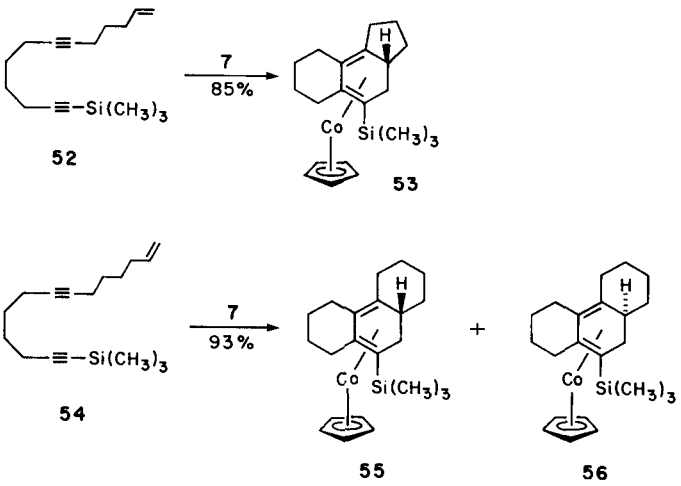
1. the regiospecific alkylation of 1,5-hexadiyne to furnish **46** and ultimately **47**,
2. the stereoselective alkylation of the lithium enolate derived from **48** with **47** to give **49** (two diastereomers),
3. the stereoconvergent cocyclization of **49** to construct steroid **50** stereospecifically,
4. the regiospecific protodesilylation at C-2 of **50**, and
5. the oxidation of ring A to furnish racemic estrone.

The target molecule **51** is formed in five steps from 2-methylcyclopentenone (21% overall yield), and in six steps from 1,5-hexadiyne (14%). The ketal derived from **49** gives even better cyclization yields. Unfortunately, a more direct approach to the A-ring phenol present in estrone by cocyclization of **49** with alkoxyalkynes was not regioselective and suffered from catalyst depletion by cyclobutadiene formation[61].

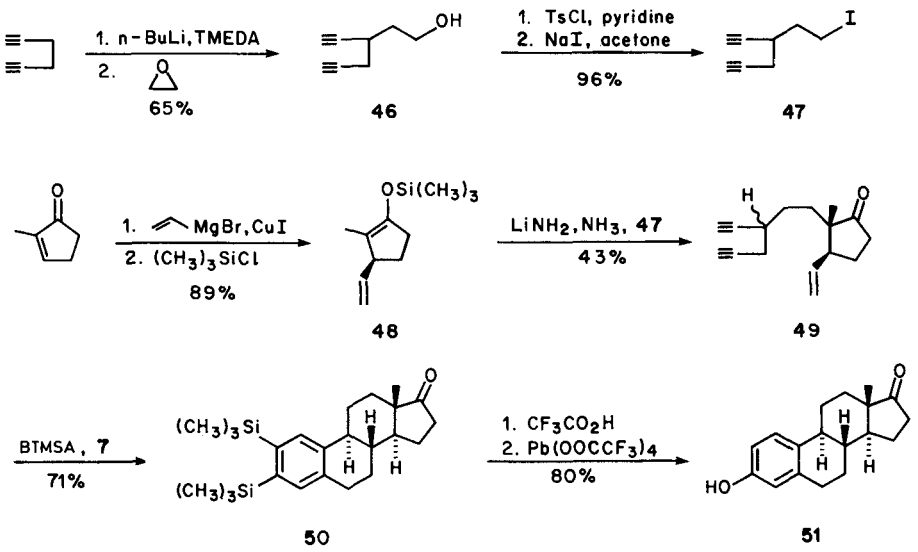
5. [2+2+2]-Cycloadditions of Enediynes: Stereospecific One-Pot Synthesis of Tri- and Tetracyclic Diene Complexes

5.1. Intramolecular Cyclizations of Enediynes with a Terminal Double Bond

Entry 3 in Scheme 3 indicates the potential utility of a cocyclization in which an alkene is employed. The synthetic versatility of such a transformation becomes apparent when one realizes that stereochemical consequences, e.g., ensue upon transformation of a stereochemically defined double bond. There are indeed various organometallic compounds which catalyze such reactions[29], one of which is based on the stoichiometric reaction of $CpCo(CO)_2$ leading to cyclohexadiene complexes[62]. In order to establish the utility of such a method, purely intramolecular cyclization reactions were chosen involving terminal alkenes. Scheme 24 shows examples of the success-

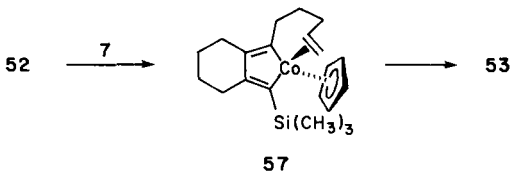


Scheme 24. Intramolecular cyclizations of enediynes with terminal double bonds.



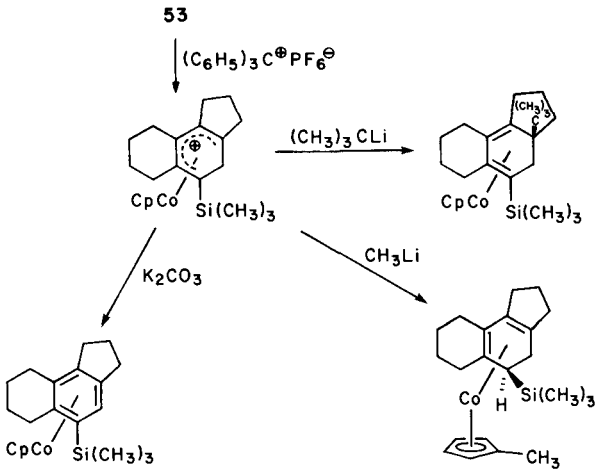
Scheme 23. A $CpCo(CO)_2$-catalyzed synthesis of (±)-estrone.

ful outcome of these attempts[29,63]. Interestingly, complete stereoselectivity is observed in some cases, its utter absence in others. Thus, **52** leads only to diastereomer **53**, whereas the homologue **54** gives an equimolar mixture of **55** and **56**. Why this is so remains a mystery. It is attractive to invoke an *exo*-Diels-Alder type mechanism involving a metallacycle of the type **57** leading to **53** (Scheme 25). However, insertion pathways and kinetic metallacyclopentene[64] formation cannot be ruled out as alternatives, and it is not clear why merely extending the appendant sidechain by one carbon should completely eradicate any selectivity. More puzzling, the desilylated analogue of **52** is equally unselective in its reactions.



Scheme 25. Diels-Alder-like mechanism for the reaction **52**→**53**.

Regardless of this mechanistic question, the method provides an efficient preparation of hitherto inaccessible polycyclic dienes, liberated almost quantitatively from their complexes by oxidative demetalation[63]. Some preliminary indication has been gathered that dienylsilane moieties such as those present in the cyclization products **53**, **55**, and **56** may be useful masked functional groups, for example α,β-unsaturated enones[63].

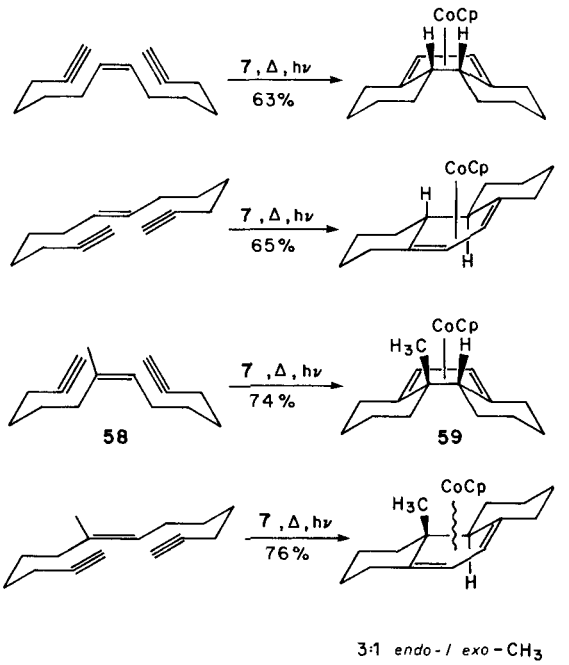


Scheme 26. Attack by nucleophiles on CpCo-cyclohexadienyl cations.

The presence of the metal may be beneficial. It protects the diene from rearrangements, polymerization, and (when applicable) protodesilylation. As observed for the analogous isoelectronic tricarbonyliron systems[65], hydride abstraction can be effected with trityl hexafluorophosphate to give cations which are subjectable to nucleophilic attack (Scheme 26). However, the regioselectivity[66] appears unpredictable.

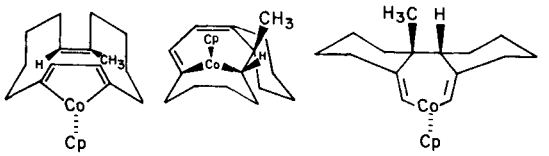
5.2. Intramolecular Cyclizations of Enediynes with Internal Double Bonds: Stereochemistry of the Double Bond

With the demonstration of the successful cyclization of terminal enediynes, it became necessary to establish the scope of the reaction by testing more highly substituted systems, particularly those in which the stereochemical fate of the double bond could be determined. For this purpose a series of internal enediynes was subjected to the cyclization conditions, altered to include photochemical acceleration of CO dissociation (Scheme 27)[67]. It can be seen that



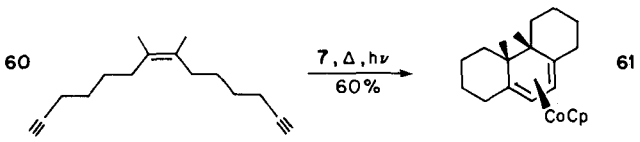
Scheme 27. Intramolecular cyclizations of enediynes with internal double bonds.

these transformations proceed relatively efficiently and with remarkable stereoselectivity, both with respect to the stereochemistry of the original double bond and the stereochemistry at cobalt. For example, of the four possible diastereomers, the enediyne **58** forms only one, namely **59**. The observed selectivity is consistent with mechanisms in which either an enyne unit or the two ethynyl groups undergo initial coupling. Subsequent incorporation of the third unsaturated moiety may then occur by Diels-Alder or insertion pathways. Some possible crucial intermediates arising from the reaction of **58** are depicted in Scheme 28, illustrating the variety of options. It appears in all cases that steric arguments can be invoked to explain the observed stereochemical results. It also transpires that, unlike



Scheme 28. Possible intermediates in the cyclization of **58**.

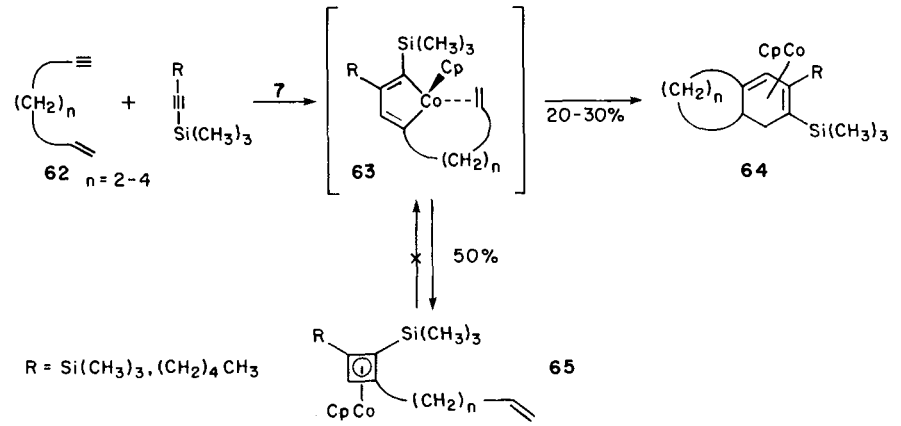
the Diels-Alder and numerous other cycloaddition reactions, the steric encumbrance of the double bond has little influence on the successful outcome of the reaction. The cyclization can therefore be used to accomplish a traditionally very difficult synthetic task: the introduction of quaternary carbon atoms into polycyclic frameworks, particularly those bearing angular methyl groups[68]. Currently, the most impressive demonstration of this potential is the conversion of the substrate **60**, which contains a tetrasubstituted double bond and, under standard conditions (see Scheme 29), affords the tricyclic diene **61** bearing two adjacent quaternary carbon atoms[69]. Surprisingly, and perhaps attesting to the (sterically induced?) relatively greater sensitivity of complex **61**, filtration through silica gel gave the free ligand in high yield.



Scheme 29. Cyclization of **60** to **61** with two adjacent quaternary centers.

5.3. Intermolecular Cyclizations of Enynes

Intramolecular [2+2+2]-cycloadditions of enediynes have found a fair amount of applications, whereas their intermolecular variants have so far been little exploited. Part of the problem appears to be the occurrence of a competing rapid valence tautomerization of the intermediate metallacyclopentadiene to give cyclobutadiene complexes. For example, cooligomerization of the α,ω-enynes **62** with BTMSA gave mainly **65** and only moderate amounts of the desired bicycle **64**[29,70] (Scheme 30). Moreover, only

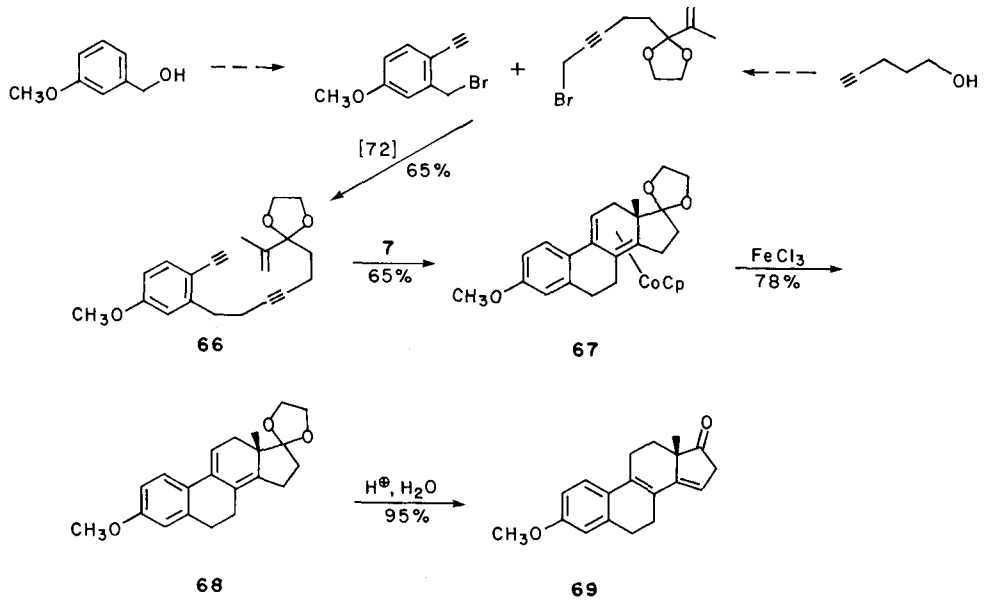


Scheme 30. Cocyclizations of α,ω-enynes with alkynes.

in the case of **64** (n=2) was stereoselectivity observed in the product. The cyclobutadienes **65** cannot, unfortunately, be induced to re-enter the cyclization manifold, regardless of the application of photochemical, thermal, or oxidative degradation methods. It appears that **63** undergoes relatively slow alkene incorporation. Complete regioselectivity is observed when 1-trimethylsilyl-1-heptyne is cocyclized with **62** (n=3, 4), suggesting that the trimethylsilyl group, as expected, prefers the α-position to the metal upon oxidative coupling to the metallacycle **63**. Improvement of the yields awaits the outcome of experiments designed to probe further the stereoelectronic aspects of the reactions.

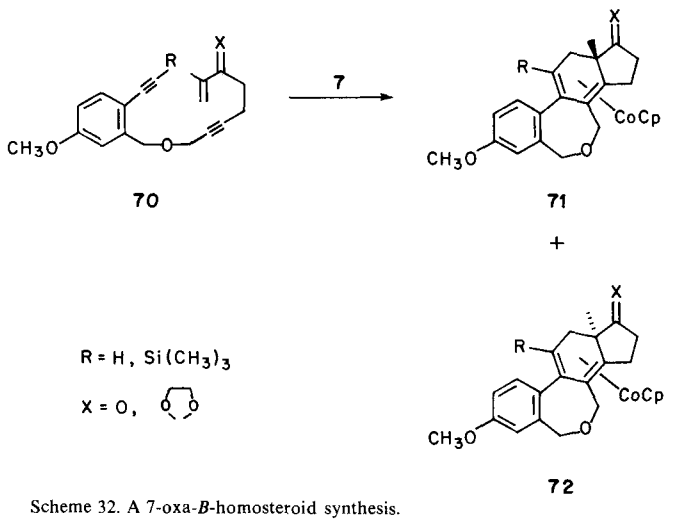
5.4. The Cobalt-Way to (±)-Estrone: the A→ABCD Approach

The effectiveness of the cycloadditions depicted in Scheme 24 suggested further application to the total synthesis of steroids in which the BCD portion of their framework would be fused to a pre-existing aromatic A-ring. This approach also provided the opportunity to test the [2+2+2]-cycloadditions of a 1,1-dialkylated olefin. With this aim in mind, the crucial enediyne precursor **66** was synthesized (Scheme 31)[71], utilizing in the key step a dihydrothiazole-mediated coupling of benzyl and propargyl halides[72]. Reaction of **66** with 7 gave the steroid complex **67** completely stereospecifically, the methyl group at C-13 being positioned *exo* to the metal. It was surprising to find that the steroidal pentaene ligand **68** had not been described in the literature prior to the present synthesis. There appear to be two reasons for this: firstly, the ligand **68** obtained on oxidative demetalation of **67** is very sensitive, turning into colorless, flocculent, insoluble material on exposure to air; secondly, the position of the diene moiety in **68** is thermodynamically disfavored over that present in **69**, into which it can be converted by acid treatment. Compound **69** is the Torgov intermediate in the synthesis of estrone[73]; its novel preparation as in Scheme 31 constitutes another formal total synthesis of the racemic natural product. Mechanistically, one could again invoke a Diels-Alder cycloaddition of the type depicted in **57** to account for the stereoselectivity observed. The added bulky ketal group would ensure that the chain connecting diene to dienophile would be placed *exo*.



Scheme 31. Steroid synthesis by enediyne cyclization.

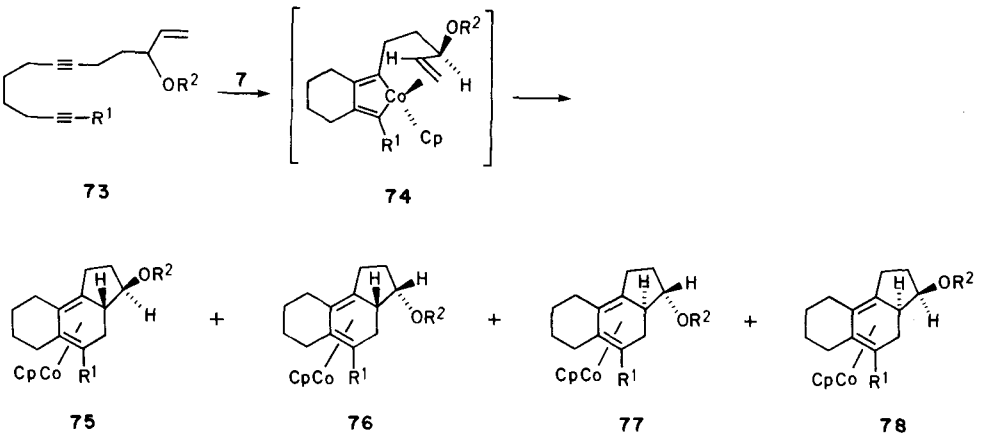
Similar arguments could be advanced to explain the changes in selectivity encountered in the transformations of **70** into the 7-oxa-*B*-homosteroid complexes **71** and **72** (Scheme 32)[71]. For example, when $R=(CH_3)_3Si$, the ketalized system **70** ($X=OCH_2CH_2O$) produces only **71** (analogous to the conversion of **66** into **67**), whereas the ketone **70** ($X=O$) leads to a mixture of **71** and **72** in which the latter predominates. This finding is possibly a consequence of the preferred *endo*-arrangement of the carbonyl group in the transition state for addition.



Scheme 32. A 7-oxa-*B*-homosteroid synthesis.

5.5. Diastereoselective Cyclizations of Chiral Substrates

Since the [2+2+2]-cycloaddition of achiral enediynes leads to the formation of ligands containing new chiral centers, it was of interest to investigate the potential diastereoselectivity of such a process with chiral substrates. In particular, it was hoped that a mechanistic insight might be gleaned from the reaction of **73**, for, if a Diels-Alder-like process involving **74** was operating, steric arguments would have to place the substituent OR^2 *exo* (as shown and as seen in general in intramolecular reactions of this type), ultimately furnishing only **75** (Scheme 33) at the ex-



Scheme 33. Diastereoselective cyclizations of enediynes.

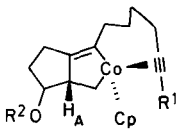
pense of the other three possible diastereomers **76**—**78**. However, as the results in Table 1 show[74,75], the outcome

Table 1. Yields of Complexes **75**–**78**.

R^1	R^2	Relative yields [%]				Isolated	t
		75	**76**	**77**	**78**	yields [%]	[h]
$Si(CH_3)_3$	CH_3	71	26	—	3	88	4
$Si(CH_3)_3$	$C_6H_5CH_2$	73	23	—	4	85	4
$Si(CH_3)_3$	CH_3OCH_2	69	24	—	7	91	4
$Si(CH_3)_3$	tBuSi$(CH_3)_2$	36	52	—	12	94	6
$Si(CH_3)_3$	$Si(i$Pr$)_3$	37	39	6 [b]	18 [b]	88	24
$Si(CH_3)_3$	tBuSi$(C_6H_5)_2$	33 [b]	47 [b]	—	20 [b]	[a]	[a]
tBuSi$(CH_3)_2$	tBuSi$(CH_3)_2$	35	50	—	15	91	6

[a] 44% conversion after 24 h. [b] Not isolated; presence ascertained by NMR spectra.

of this experiment appears to confuse the issue rather than to clarify it. Thus, although the first three entries appear to bear out the premise of Scheme 33, introduction of bulkier OR^2-groups, expected to maximize the intermediacy of a species of the type **74** and hence the yield of **75**, has exactly the opposite effect. Whether this phenomenon is general for non-silicon-containing groups has yet to be ascertained. The observed results, at odds with the simple Diels-Alder picture, might be more readily explained by invoking **79** as an intermediate formed by initial enyne coupling. Models show that **79** adopts a pseudo-chair config-

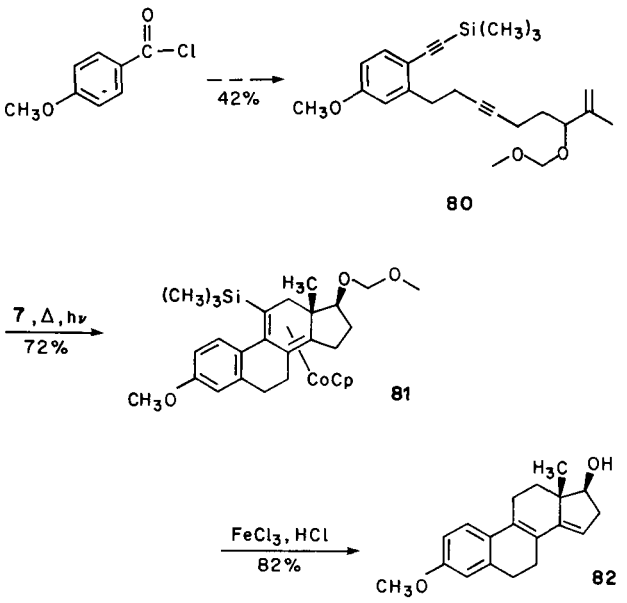


79

uration, placing the OR^2 substituent in an initially favorable equatorial position. Upon oxidative coupling, this group emerges severely eclipsed with H_A. This effect would lead to the OR^2-moieties increasingly preferring to be positioned axially with increasing bulkiness, or to the formation of a boat-shaped transition state in which the prochiral vinyl hydrogen points towards the metal (giving appreciable amounts of **77** and **78**, in addition to **75** and **76**, as observed).

5.6. A Diastereoselective Steroid Synthesis

The fairly selective outcome of at least some of the examples in Table 1 can be exploited in a diastereoselective steroid construction as shown in Scheme 34[75]. The required precursor **80** is readily prepared in good overall yield starting from *p*-methoxybenzoyl chloride. Cyclization gives mainly **81** (72%) in addition to its 17α-isomer (20%). Oxidative demetalation under acidic conditions converts **81** directly into the known estrapentaenol **82**[76], by (presumably in this sequence) loss of metal, diene isomerization, protodesilylation, and removal of the alcohol protecting group. The free ligand is also obtainable from **81** (81%), and in contrast to **68**, is air stable. A curious feature



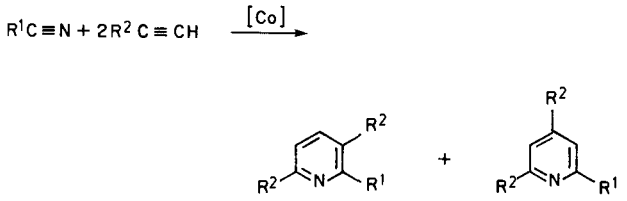
Scheme 34. Diastereoselective steroid synthesis.

of complex **81** (but not observed in the free ligand) is the presence of hindered rotation of the trimethylsilyl group ($\Delta H^{+} = 18.8$ kcal/mol) on the NMR time scale, the first such impaired mobility observed for a vinyltrimethylsilane[77], obviously caused by the bay-region hydrogen at C-1.

6. The Cobalt-Way to Heterocyclic Systems

6.1. Cocyclization of α,ω-Diynes with Nitriles: Synthesis of Cycloalka[1,2-*c*]pyridines and a Total Synthesis of Vitamin B_6

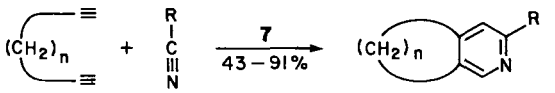
In the early 1970s, several groups independently discovered that cobalt complexes could cocyclize alkynes with nitriles to furnish pyridines in stoichiometric and catalytic reactions (Scheme 35)[78]. *Bönnemann* et al. have carried



Scheme 35. Cobalt-catalyzed pyridine synthesis.

out a comprehensive study of the scope and limitations of this reaction[79]. Although good control of chemoselectivity is obtained in the preparation of 2-substituted pyridines, product mixtures are formed in the cocyclization of unsymmetrical alkynes (Scheme 35)[79]. This potential prob-

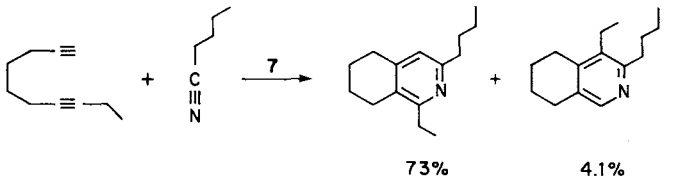
lem can be avoided by the use of α,ω-diynes (Scheme 36),



n = 3–5, R = alkyl, aryl, CH_2OCH_3, $CH_2CO_2C_2H_5$

Scheme 36. Cocyclization of α,ω-diynes with nitriles.

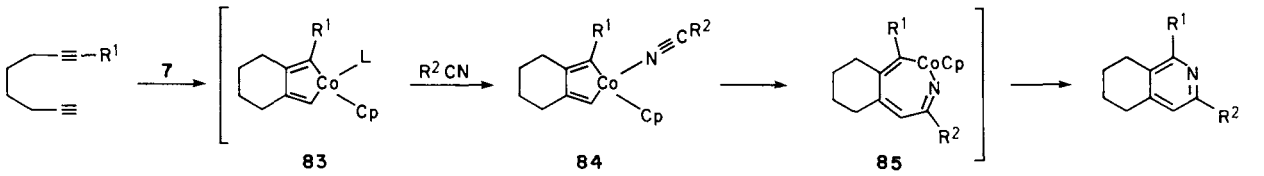
in which regioselectivity is controlled by the chelating nature of the alkyne component and by steric effects, whereas chemoselectivity is apparently controlled by electronic interactions[80]. Unsymmetrical diynes lead to predominant generation of the sterically less encumbered substitution pattern (Scheme 37). With electron-deficient ni-



Scheme 37. Regioselective cocyclization of unsymmetrical diynes with nitriles.

triles, the reaction fails to give satisfactory yields of pyridines, furnishing instead diyne oligomers. On the other hand, with other nitriles it is remarkably chemospecific, requiring only equimolar amounts of starting materials[80].

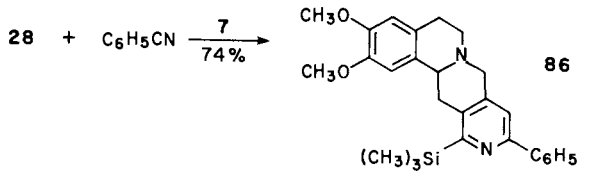
Mechanistically, the above results are readily accommodated by invoking initial formation of the metallacycle **83** (Scheme 38). The Co(III) center may now be postulated to



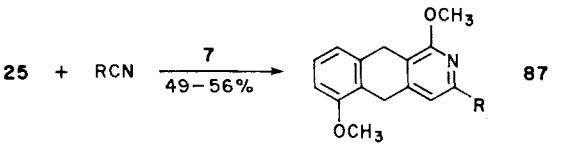
Scheme 38. Mechanism postulated for the formation of annelated pyridines.

select for nitrile by ligation through its lone pair[81], as in **84**, an interaction which becomes noncompetitive with alkyne complexation in the case of electron-deficient nitriles. Insertion into the less hindered cobalt-carbon bond, placing the nitrogen next to cobalt (**85**), eventually furnishes the observed products. This mechanism is consistent with the finding that isolated cobaltacyclopentadienes react like **83**[78a] and lead to substituent patterns similar to those observed in normal pyridine formation[79]. However, there is no conclusive evidence ruling out other pathways.

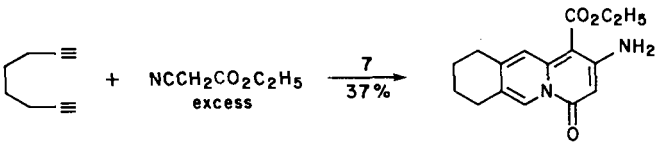
Irrespective of the mechanistic questions, the cocyclization depicted in Scheme 36 is potentially synthetically useful. For example, the diyne **28** cotrimerizes regioselectively



with benzonitrile to give **86**[36], an example of the rare isoquino[2,1-*b*]-2,6-naphthyridine nucleus. Similarly, the 2-azaanthracene framework **87** is accessible from **25**[35].



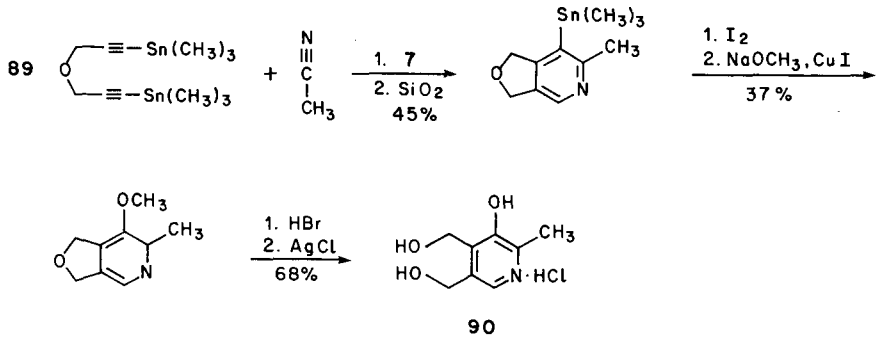
Employment of excess ethylcyanoacetate in the cocyclization with diynes can lead to further condensation of the intermediate 2-pyridylacetic esters[82]. This facilitates the one-pot synthesis of annelated quinolizinones such as **88**[35,80].



Dipropargylamines[83] and dipropargyl sulfides[83a] have been successfully cocyclized to give the corresponding 1,3-dihydropyrrolo- and thieno[3,4-*c*]pyridines. Based on this principle, but using dipropargyl ether **89** as starting material, a regioselective synthesis of vitamin B_6 **90** has been accomplished (Scheme 39)[84]. The cyclizations of **89** are the first to employ stannylalkynes, necessary in this case to ensure the successful outcome of electrophilic aromatic substitution on the resulting stannylpyridine.

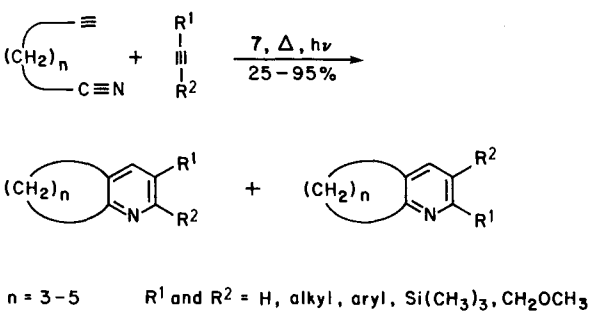
6.2. Cocyclization of ω-Alkynyl Nitriles with Alkynes: Synthesis of Cycloalka[1,2-*b*]pyridines

Scheme 40 shows a complementary cyclization strategy which enables the preparation of [*b*]annelated pyridines[85]. Regioselectivity is again attained in the case of unsymmetrical alkynes, the bulky substituent emerging next to the nitrogen. The successful outcome of this reaction appears

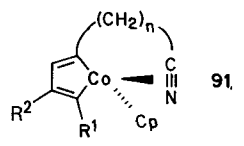


Scheme 39. A cobalt-catalyzed synthesis of vitamin B_6.

to depend on the efficiency of oxidative coupling to **91**, the larger group on either of the original alkynes being located in the α-position to the metal. The trimethylsilyated pyridine derivatives can be further functionalized by electrophilic aromatic substitution. A recent extension of Scheme 40 has involved the cyclodimerization of two ω-alkynyl nitrile molecules to give the corresponding cyanoalkyl-substituted cycloalka[*b*]pyridines[86]. Finally, it should be pointed out that cyclopentadienylcobalt does not appear to be capable of coupling more than one nitrile group in these transformations. This contrasts with $Fe_2(CO)_9$, which facilitates the cocyclization of adiponitrile with nitriles to give 1,2,4-triazines[87].



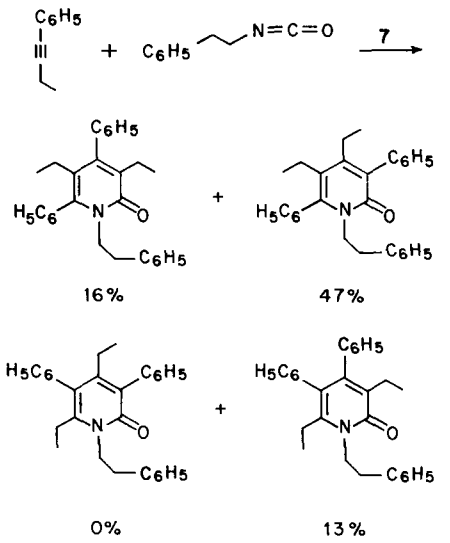
Scheme 40. Cocyclization of ω-alkynyl nitriles with alkynes.



91

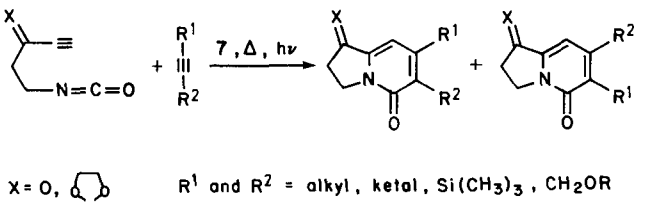
6.3. Cocyclizations of ω-Alkynyl Isocyanates: a Total Synthesis of Camptothecin

In analogy to the topological change occurring when going from alkynes to alkenes in [2+2+2]-cycloadditions, the employment of an imine unit instead of a nitrile in cocyclizations with alkynes could provide a ready synthetic entry to dihydropyridines. Moreover, if the C=N-substructure were to be incorporated into an α,ω-doubly unsaturated chain, its cyclization could lead to the rapid construction of polyheterocyclic systems incorporating bridgehead nitrogen atoms. Although this goal remains to be realized with simple imines[88], isocyanates appear to be suitable substrates in such an endeavor[79,89]. In simple cocyclizations leading to substituted pyridones (Scheme 41)[88]



Scheme 41. Product distribution in the cocyclization of β-phenethyl isocyanate with 1-phenyl-1-butyne.

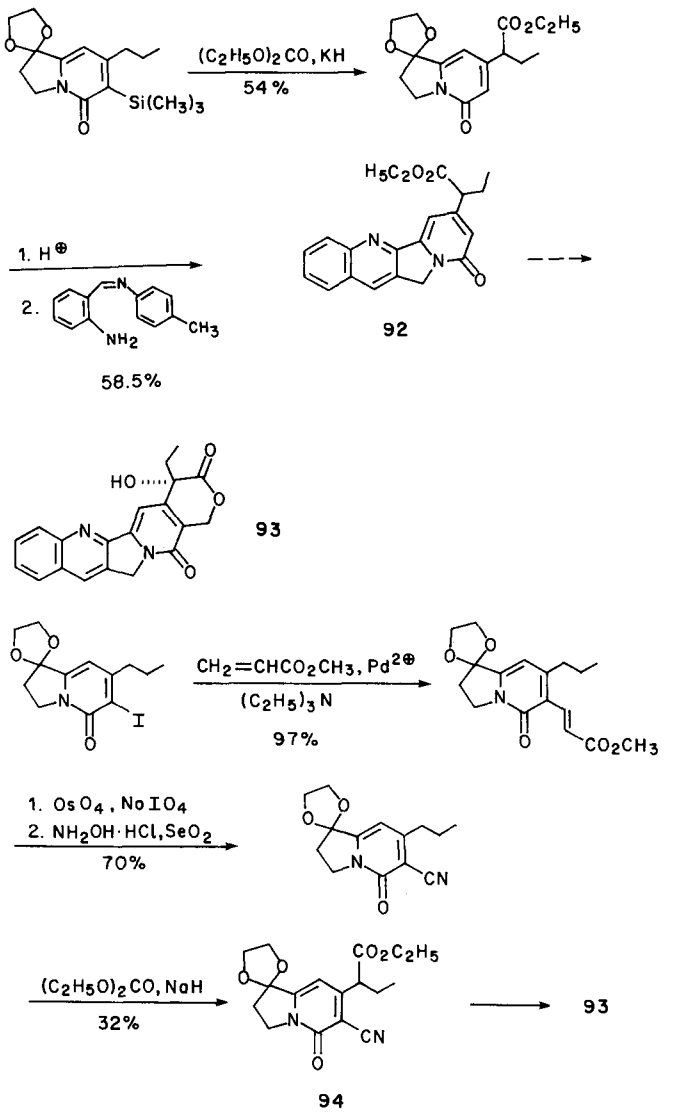
there is a potential problem of regioselectivity[79,88,89]. However, it may be circumvented by the use of ω-alkynyl isocyanates (Scheme 42)[90]. Good chemo- and regioselectivity are observed, the latter favoring the bulky substituent (particularly trimethylsilyl) taking up the α-position to the carbonyl group. An intermediate of the type **91** is indicated, but bearing an appendant complexed isocyanato rather than a nitrile group. Unexpectedly, based on steric



Scheme 42. Cocyclization of ω-alkynylisocyanates with alkynes.

considerations, the trimethylsilyl group always wins out and takes over the α-position, even when in competition with a *tert*-butyl group. This finding clearly indicates the operation of both steric and electronic effects with the silyl substituent (see Section 2.4). The silyl moieties in the product allow for selective halodesilylations at C-6[90]. In contrast, the halogenation of ordinary 2-pyridones leads to mixtures[91]. Finally, carbon-carbon bond formation is possible at C-6 by employing palladium-catalyzed coupling reactions of the corresponding 6-iodides[52,92].

Application of the above methodology has led (Scheme 43)[90] to two formal syntheses of the antitumor alkaloid camptothecin **93**[93]; one proceeds via the intermediate **92**[94], the other via **94**[95].



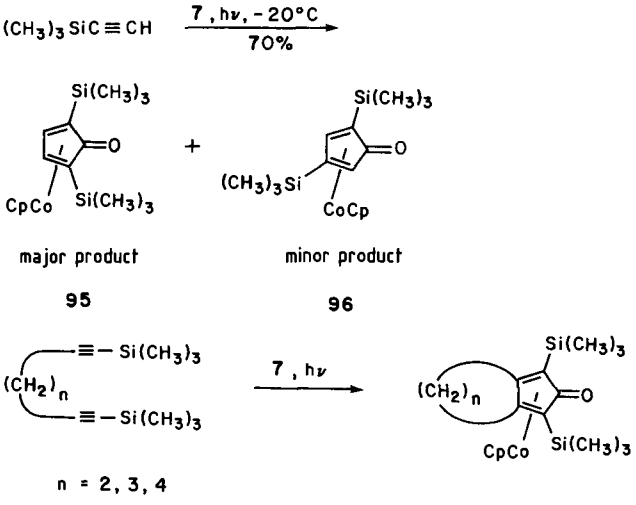
Scheme 43. Two total syntheses of camptothecin.

It is interesting to note that bis(η^4-cyclooctadiene)nickel, another catalyst reported to catalyze the formation of pyridones from alkynes and isocyanates[96], gives not only a different product distribution in the case depicted in Scheme 41, but is also a much poorer catalyst than the cobalt system in the presence of terminal alkynes[88]. Evidently, a different mechanism is operating in this system.

7. [2+2+2]-Cycloadditions Involving Carbon Monoxide: Cyclopentadienone Formation

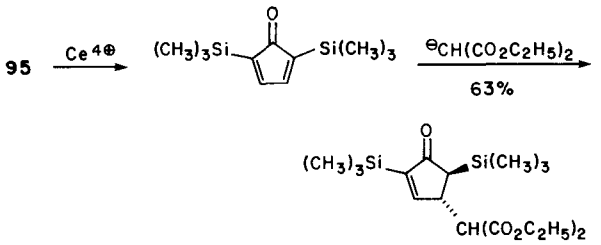
7.1. Synthesis of Cyclopentadienones

An alternative to the mode of cyclization depicted in Scheme 3 is provided by cyclization partners with "carbenoid" atoms, such as isocyanides[97] and carbon monoxide[13c,98]. If multiple insertion pathways could be avoided and product selectivity were controlled, the CpCo moiety should enable a [2+2+2]-cycloaddition to give five-membered ring systems in the presence of either substrate[13e,99]. Although isocyanides have not yet proven successful[100], it has been found that trimethylsilylalkynes undergo such reactions under low-temperature photolytic conditions in the presence of stoichiometric amounts of $CpCo(CO)_2$ **7** to furnish complexed cyclopentadienones regioselectively (Scheme 44)[101].



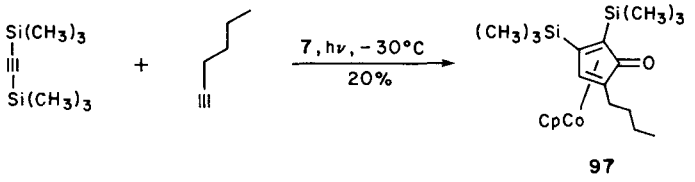
Scheme 44. Formation of cyclopentadienone complexes.

The utility of these complexes lies in their ready decomplexation ($Ce^{4\oplus}$) to give the free monomeric cyclopentadienones, which function as extraordinarily reactive substrates in further transformations (Scheme 45)[102].



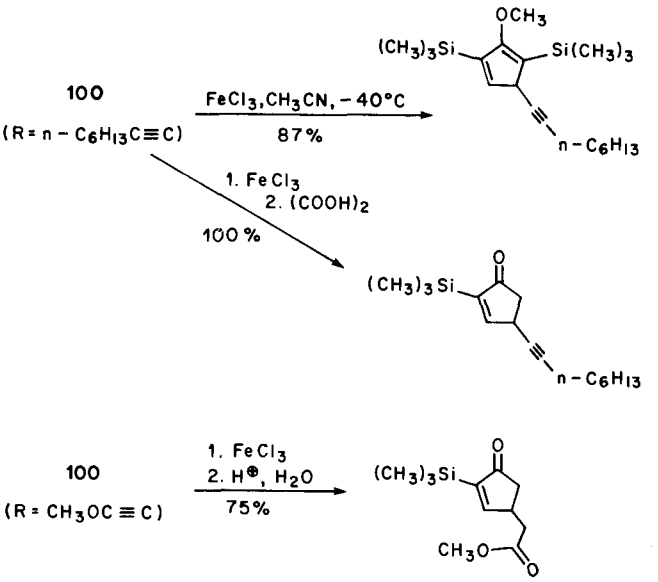
Scheme 45. Nucleophilic addition to 2,5-bis(trimethylsilyl)cyclopentadienone.

Metallacyclopentadienes[17,26], metallacyclobutenones[98,103], and more complex intermediates[103] have been invoked in the formation of cyclopentadienones from alkynes and carbonylmetal compounds. All are consistent with the observed product regioselectivity. For example, **95** is the major product in the cyclization of trimethylsilylacetylene with 7 (Scheme 44). On the other hand, when $(CH_3)_5C_5Co(CO)_2$ was employed, the corresponding 2,4-disilylated product predominated[101].



97

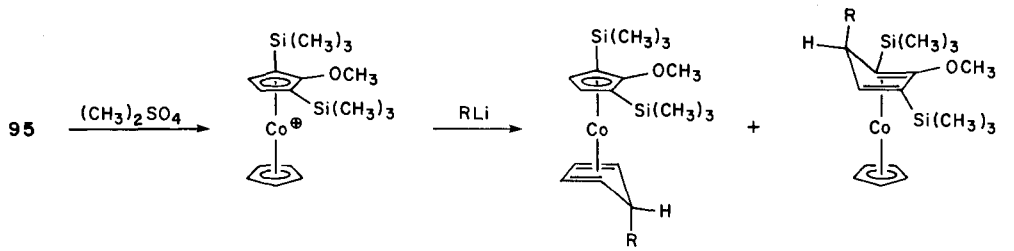
Cocyclization of 1-hexyne with BTMSA results in **97** as the exclusive cotrimer[102], indicating further synthetic potential, although the yield is, as yet, unsatisfactory.



Scheme 47. Oxidative decomplexation of the substituted ligands in **100**.

7.2. Cobaltocenium Salts as Precursors of Substituted Cyclopentadienes and Cyclopentadienones

Cyclopentadienone complexes of the type **95** can be exploited synthetically if they are activated by methylation to give cobaltocenium salts[104]. In the case of **95**, the resulting cation **98** can be ring-selectively and regioselectively attacked by organolithium reagents to give predominantly either **99** (R = bulky substituent, alkyl) or **100** (R = small substituent, alkynyl) (Scheme 46)[105]. It is the latter which



98 99 100

Scheme 46. Nucleophilic additions to cobaltocenium salts.

commands synthetic attention, because highly substituted and functionalized cyclopentadienes or cyclopentenones may be liberated from these species under mild oxidizing conditions (Scheme 47)[105]. Five-membered ring compounds of this type should be useful in the construction of cyclopentanoid natural products[106].

8. Conclusions and the Future

It is clear that the present methodology has not only provided some powerful simplifications in approaches to the construction of natural and medicinal products, but has also given access to novel structures of theoretical and synthetic interest. Chemo-, regio-, and stereospecific cyclizations in conjunction with the use of auxiliary groups, such as for example silicon- or tin-based substituents, allow for the rapid build-up of polycyclic ring systems with extensive control of ring-substitution. However, much remains to be done. The synthetic potential of such [2+2+2]-cycloadditions, as outlined in Scheme 3, has only barely begun to be explored. Many additional unsaturated organic (and organometallic?) substrates could be envisaged to participate in such a reaction. The possible stereochemical complexity of cyclizations involving increasing numbers of double-bonded partners should be elucidated. There must be a host of other catalysts, waiting to be discovered, which might exhibit specific selectivities. The use of optically active ligands in enantioselective transformations should be explored. Novel structures incorporating unusual strain-related and electronic features will become available, and their chemistry should provide further insight into the theories of bonding, delocalization, and aromaticity. Finally, why stop at [2+2+2]? There are many other combinations of one, two, and higher atomic synthons which might be induced to undergo multiple bond-formations in the presence of the appropriate catalyst to supply structures of increasingly higher complexity. Such will be the task of future investigators and collaborators.

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Chelation or Non-Chelation Control in Addition Reactions of Chiral α- and β-Alkoxy Carbonyl Compounds

New Synthetic Methods (44)

By Manfred T. Reetz*

The addition of C-nucleophiles such as Grignard reagents or enolates to chiral α- or β-alkoxy aldehydes or ketones creates a new center of chirality and is therefore diastereogenic. In order to control stereoselectivity, two strategies have been developed: 1) Use of Lewis-acidic reagents which form intermediate chelates, these being attacked stereoselectively from the less hindered side *(chelation control)*; 2) use of reagents incapable of chelation, stereoselective attack being governed by electronic and/or steric factors *(non-chelation control)*. Generally, the two methods lead to the opposite sense of diastereoselectivity. It is possible to predict the outcome by careful choice of organometallic reagents containing elements such as Li, Mg, B, Si, Sn, Cu, Zn, or Ti.

1. Introduction

The two π-faces of a carbonyl compound having at least one chiral center are diastereotopic. Addition of C-nucleophiles such as Grignard reagents or enolates can therefore lead to unequal amounts of diastereomers. Reactions involving such 1,n-asymmetric induction[1b,c] have been termed "diastereofacially selective"[2]. Although this phenomenon was observed as early as 1894[1], it was not until the work of *Cram* et al. that some degree of systematization was attempted[3]. In what is now known as Cram's rule[1], an α-chiral aldehyde (or ketone) such as **1**[*] is assumed to adopt a conformation in which the largest of the three α-substituents is antiperiplanar to the carbonyl function, nucleophilic attack then occurring from the less hin-

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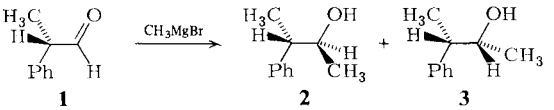
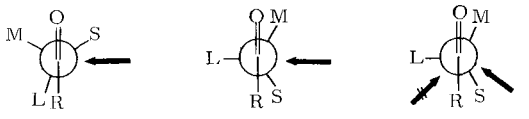
[*] Only one enantiomer is shown, although a racemate was used leading to racemic products.

dered side. In the case of CH_3MgBr, the ratio of Cram to anti-Cram products **2** : **3** turned out to be ca. 66 : 34[1,3]. Besides the Cram model (cf. Newman projection **4**), other explanations have been offered[1]. *Felkin* et al. assumed a reacting conformation **5**[4], a model which has been refined by *Anh*, who postulated *non-perpendicular* attack (Bürgi-Dunitz trajectory), as shown in **6**, on the basis of molecular orbital considerations[5].



1 **2** **3**

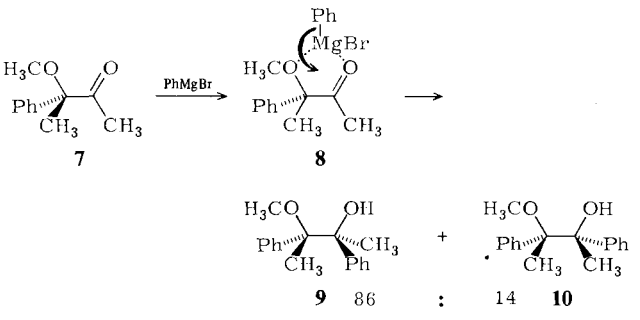


4 **5** **6**

L = large, M = medium, S = small substituent

For carbonyl compounds with α-halogen substituents, *Cornforth* et al. proposed an electrostatic model in which the electronegative group points away from the polar carbonyl function, i.e., it takes the place of L in **4**[1,6]. In contrast, *Felkin et al.* stated that "polar effects stabilize those transition states in which the separation between the incoming nucleophile and the electronegative group is greatest", as in **5** (L = electronegative group)[4]. *Anh*'s MO calculations show that **6** (L = chlorine) is, in fact, the most reactive conformation because $\pi^*_{C=O}$-σ^*_{C-Cl} interaction provides a low-lying LUMO. Attack *anti* to L avoids certain anti-bonding interactions which occur in a *syn*-trajectory (see arrows in **6**)[5].

For α-alkoxy or hydroxy carbonyl compounds, the electronegative oxygen substituents exert potentially analogous effects. However, a different phenomenon is also possible, namely chelation, which makes the *opposite* π-face sterically more accessible. In such cases, *Cram*'s cyclic model pertains[1,3] (see **8**)[7].

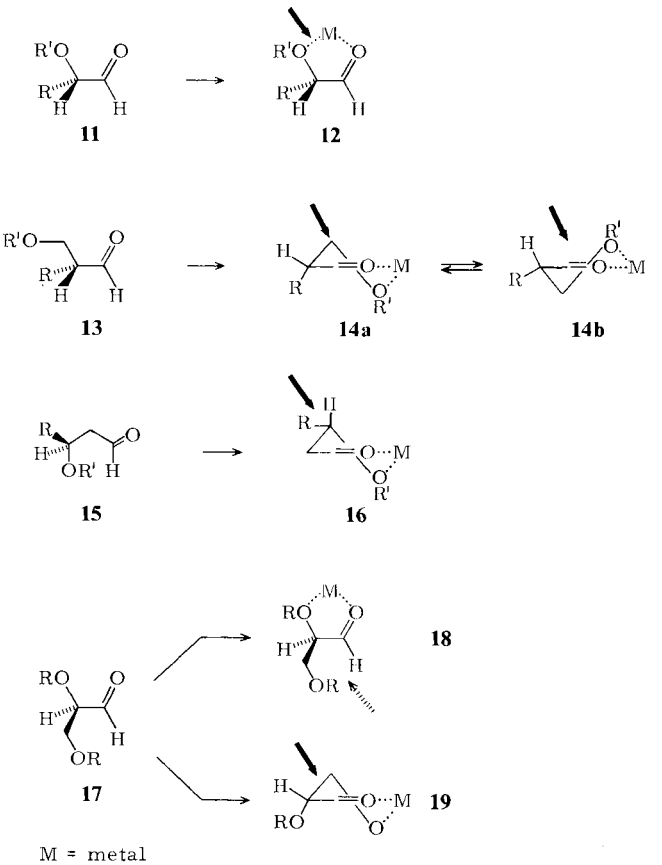


7 **8**

9 86 : 14 **10**

This review focuses on recent developments in controlling chelation or non-chelation in diastereogenic additions to α- and β-alkoxy (and -hydroxy) aldehydes and ketones. Several reviews covering certain aspects of chelation as well as other types of "acyclic stereoselection" have appeared elsewhere[1,8,9].

We shall call the respective dominant diastereomer chelation controlled or non-chelation controlled (Felkin-Anh products)[*]. The aldehydes **11**, **13**, and **15** (and the analogous ketones) react with Lewis acids to give the chelates **12**, **14a**, and **16**, respectively, the arrows indicating the preferred direction of attack. Instead of **14a**, the other half-chair conformation **14b** can also be invoked. With the dialkoxy aldehyde **17**, α-coordination leads to **18** and β-coordination to **19**, in which opposite diastereotopic faces of the carbonyl group are exposed. Chelation in **19** is analogous to that in **14a**, but diastereoselectivity might be expected to be enhanced because the non-complexed RO group facilitates an "Anh-effect". For non-chelation control, it is clear that reagents *not* capable of bidentate complexation are necessary.



11 **12**

13 **14a** **14b**

15 **16**

17 **18** **19**

M = metal

Besides 1,n-asymmetric induction, a different type of stereochemical problem may arise. If a C-nucleophile such as an enolate is prochiral, addition to an *achiral* aldehyde creates two new chiral centers by linkage of two sp^2-hybridized C atoms. Diastereodifferentiation in such a process has been termed "simple diastereoselectivity", and forms the basis of most of the recent work on aldol reactions[10] and related additions of crotylmetal compounds[11].

If the aldehyde is *chiral*, such as **11**, **13**, **15**, or **17**, this type of stereoselection and the problem of diastereofacial selectivity (chelation or non-chelation) are both relevant. Thus, a maximum of *four* diastereomers may be formed. In the absence of special effects, the rules for predicting sim-

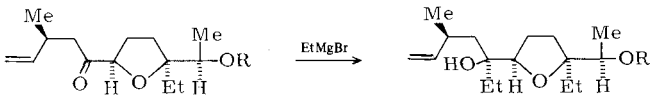
[*] The latter has sometimes been called the anti-Cram product. However, this may cause confusion because the term was first used for *Cram*'s acyclic model (e.g., **1**→**2**).

ple diastereoselection for achiral aldehydes[10,11] also apply to chiral compounds. Efficient methods for stereoselective Grignard and aldol additions to chiral alkoxy carbonyl compounds are of importance for the synthesis of natural products, e.g. ionophores, pheromones, and carbohydrates[2,8,9].

2. Chelation-Controlled 1,2-Asymmetric Induction

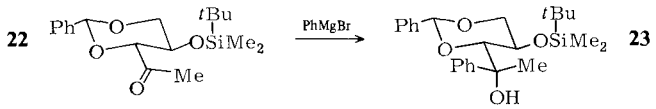
2.1. Grignard, Alkyllithium, and Cuprate Reagents

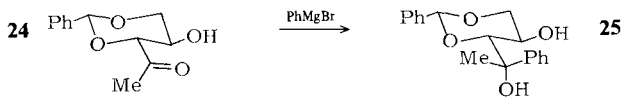
In early work *Cram* et al.[3,7] and later *Stocker* et al.[12] studied the addition of RMgX and RLi to α-alkoxy (and hydroxy) carbonyl compounds and were able to rationalize most of the data by assuming chelation of the type **12**. The ratio of chelation- to non-chelation-controlled products ranged between 55:45 and 96:4. Exceptions were "explained" by invoking competition between cyclic, dipolar, and open-chain models. Thereafter, further examples of more or less useful levels of diastereoselectivity became known[1,13]. Generally, low temperatures are beneficial, although the converse has been observed[14]. An example involving complete chelation control was reported by *Kishi* et al., **20** → **21** being one of the key steps in their synthesis of the isolasalocid ketone[15].



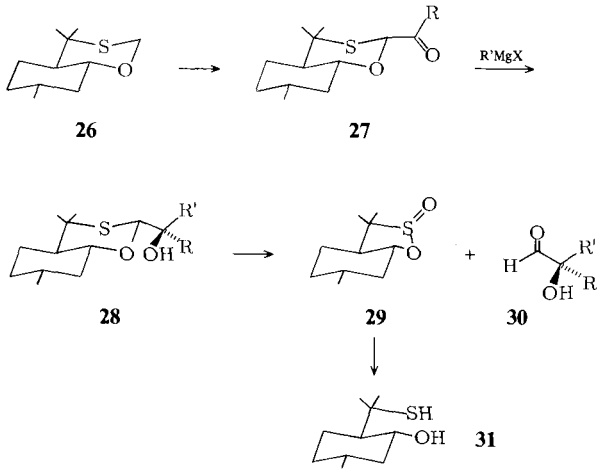
20 **21**

Horton et al. have described reactions in which the choice of protecting groups controls the sense of stereoselectivity[16]. Ketone **22** reacts with phenylmagnesium bromide to form **23** via α-coordination; the β-oxygen carries a bulky silyl group which prevents competitive β-coordination. In case of **24**, use of excess Grignard reagent first deprotonates the hydroxy group, the intermediate Mg-alkoxy moiety then inducing β-chelation. A number of α-alkoxy and α-hydroxy aldehydes and ketones in steroids have been shown to undergo pronounced chelation-controlled Grignard-type additions[8,17], but exceptions are known[18].

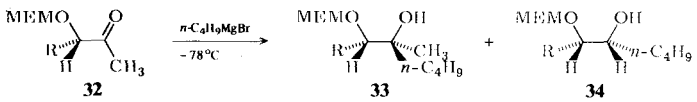




In all these cases, the old and the newly created chiral centers form part of the target molecule. It is also possible to destroy the original chiral center via some sort of cleavage (sacrificial asymmetric synthesis). For example, several groups have reported stereoselective Grignard additions to certain carbohydrates followed by oxidative cleavage, a sequence which creates a new chiral center at the expense of the old one[1,9,19]. However, if the chiral adjuvant is expensive, this is unacceptable. Recently, *Eliel* et al.[9,20] and *Mukaiyama* et al.[21] have devised ingenious systems which solve this problem. The starting point of *Eliel*'s strategy is the conversion of **26** (available from (+)-pulegone) into **27**. Grignard addition then occurs stereoselectively via α-oxygen chelation to form **28**. The fact that α-sulfur coordination does not compete was explained using the HSAB principle. Aldehyde **30** (>90% *ee*) can be liberated and the chiral starting material **31** recovered. Other 1,3-oxathianes have also been described[9]. In the system studied by *Mukaiyama* et al., α-amino ketones in which proline derivatives are incorporated form the basis of chelation control[21].



Since chelation control is *not always* efficient[1,9,18], *Still* et al. carried out systematic studies in which the type of alkoxy group, the carbon nucleophile, solvent, and temperature were varied[22]. It was found that ketones of the type **32** fail to react stereoselectively with alkyllithium reagents (e.g., *n*-butyllithium), in contrast to Grignard compounds, and that these reactions show dramatic solvent effects, tetrahydrofuran (THF) being the medium of choice.



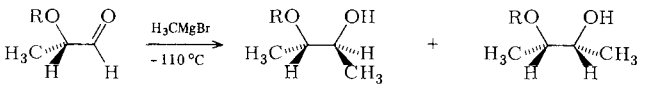
32 **33** **34**

R = *n*-C_7H_{15}
MEM = $CH_2OCH_2CH_2OCH_3$

ether	90	:	10
THF	>99	:	<1
CH_2Cl_2	94	:	6
n-C_5H_{12}	90	:	10

The methoxyethoxymethyl (MEM) group has two additional oxygen atoms, so that chelation involving a "crown-ether effect" is conceivable. However, this appears not to be necessary, since α-benzyloxy groups also facilitate complete chelation control. In their synthesis of the polyether antibiotic monensin, *Still* et al. made use of these generalities to construct one of the building blocks[23]. Another elegant application pertains to the total synthesis of (+)-zoapatanol by *Nicolaou* et al.[24]. RLi sometimes reacts more selectively than RMgX, a phenomenon which has not yet been explained mechanistically[1,9].

Unfortunately, the extremely high levels of 1,2-asymmetric induction observed with ketones do *not* extend to analogous aldehydes[25], in line with previous studies[8,9,18]. Perhaps this is due to the lower Lewis basicity of aldehydes. Thus, addition of CH_3MgBr to aldehyde **35** affords

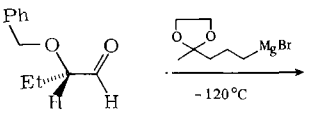


35 **36** 91 : 9 **37**

R = CH_2OCH_2Ph

36 and **37** in the ratio 91:9. Since this was the only aldehyde studied, it is not clear whether the benzylmethoxy group is necessary for the attainment of this level of selectivity.

Later experiments showed that the choice of reaction conditions, type of protecting group, and Grignard reagent are crucial, as evidenced by the fact that the α-benzyloxy analogue of **35** reacts with CH_3MgI fairly unselectively (60:40 ratio)[26]. Addition of Grignard reagents to **38** provides another example[27].



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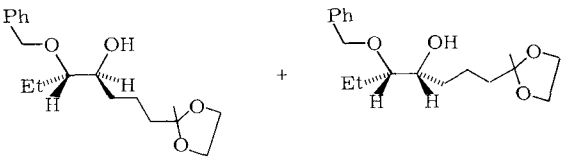
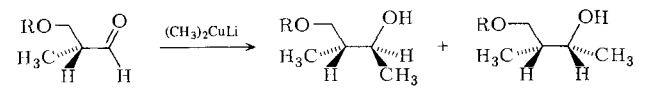


39 60 : 40 **40**

Recently, further examples of low levels of chelation control in the addition of Grignard reagents to chiral α-alkoxy aldehydes have been reported; these include compounds having various types of alkoxy groups such as methoxymethyl (MOM) and pyran moieties[13,28]. Clearly, other approaches to this problem are necessary (Section 2.3).

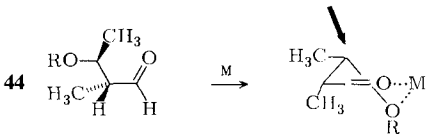
If we now consider β-coordination (see **14**), compounds of the type **41** do not react stereoselectively with RMgX or RLi, in contrast to cuprates[25]. For example, $(CH_3)_2CuLi$ adds to **41a** to afford **42a** and **43a** in the ratio 97:3. The benzyloxy analogue **41b** reacts only slightly less selectively. However, chelation-directed diastereoselectivity is not observed if the oxygen atom in the alkoxy residue is sufficiently hindered, as in the *O*-trityl derivative **41c**[25].



41 **42** **43**

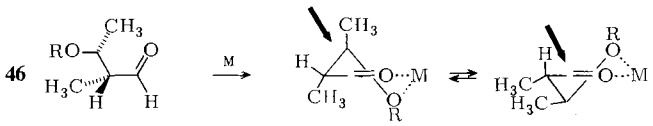
a, R = CH_2OCH_2Ph	97	:	3
b, R = CH_2Ph	95	:	5
c, R = CPh_3	≈ 33	:	67

It is unclear why cuprates, but not RMgX or RLi, lead to efficient β-chelation[25]. Nevertheless, **14** is a useful model since it also predicts stereoselectivity for compounds having an additional chiral center at the β-position. Thus, **44** shows the usual diastereofacial selectivity with $(CH_3)_2CuLi$ (>95:5), whereas **46** gives a product ratio of 2:1[25]. Although the authors do not provide a reason for this dramatic difference, chelation of **46** in a manner analogous to **45** gives rise to **47a**, in which the axial β-methyl group hinders the incoming nucleophile. An alternative conformation **47b**, in which the two methyl groups are equatorial, is also likely to react less stereoselectively than **45**.



44 **45**

R = CH_2OCH_2Ph



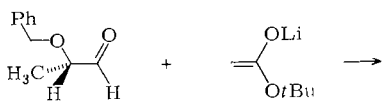
46 **47a** **47b**

R = CH_2OCH_2Ph; M = metal

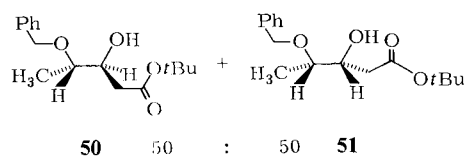
In summary, notable advances have been made in inducing chelation with the aid of RMgX, RLi, and R_2CuLi. However, a number of problems persist, and the present level of mechanistic understanding is unsatisfactory. The role played by the aggregation state of the reagents or type of solvent are poorly understood. In carbohydrate chemistry (Section 5), the situation is sometimes even less clear.

2.2. Aldol Additions with Lithium- and Magnesium-Enolates

With a few exceptions, lithium enolates add to α-alkoxy aldehydes either completely unselectively or show some degree of non-chelation control[10] (Section 4). For example, **48** reacts with the ester enolate **49** without any diastereofacial selectivity[10].

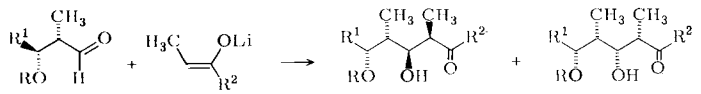


48 **49**



50 50 : 50 **51**

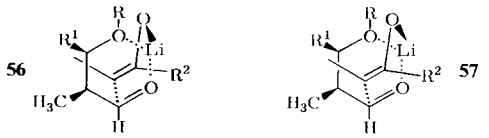
In contrast, certain β-alkoxy aldehydes having centers of chirality at the α- or β-position display useful levels of chelation control, as shown by *Masamune* et al.[29]; since they used prochiral enolates, simple diastereoselectivity is also involved. Several aldehydes **52** were allowed to react with



52 **53** **54** **55**

R = CH_2OCH_2Ph

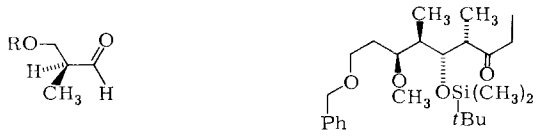
R^1	R^2			
H	Et	80	:	20
H	*cyclo*-C_6H_{11}	78	:	22
Et	Et	83	:	17
Et	*cyclo*-C_6H_{11}	90	:	10
*i*Pr	Et	87	:	13
*i*Pr	*cyclo*-C_6H_{11}	92	:	8
*t*BuMe$_2$SiOCH$_2$CH$_2$	Et	93	:	7
*t*BuMe$_2$SiOCH$_2$CH$_2$	*cyclo*-C_6H_{11}	95	:	5



56 **57**

enolates **53**, leading mainly to **54** and **55**, in addition to small amounts of the other two possible diastereomers. The preferred formation of **54** was explained by assuming coordination of the lithium cation by *three* oxygen atoms, as shown in **56**, rather than the sterically less favorable transition state **57**. This hypothesis neglects the state of aggregation of the enolates, but is nevertheless useful. Simple diastereoselectivity is *syn* (Masamune nomenclature) and depends upon the configuration of the enolate[10].

Chelation control in the reaction of **58** with the lithium enolate of ketone **59** is not as efficient (product ratio 75 : 25)[29]. Apparently, stereoselectivity is only pronounced if the system is "loaded" with additional groups at the β-position, as in **52** (R^1 = alkyl). This is plausible on the basis of the model shown in **56**. Chelation control is expected to decrease if the relative stereochemistry of the two chiral centers in **52** is reversed, but this has not been tested (cf. **44** vs. **46**).



58, R = $CH_2OCH_2CH_2SiMe_3$ **59**

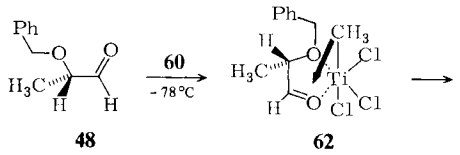
Why do α- and β-alkoxy aldehydes show such different behavior in classical aldol additions? Perhaps the Masamune decalin-like transition state in the β-case is energetically favored relative to the more strained hydrindane-like transition state which would have to be transversed in case of α-alkoxy aldehydes. It should be noted that lithium enolates derived from esters generally do not show chelation effects in reactions with β-alkoxy aldehydes (Section 4), the reason for this being unclear[10]. Systematic studies involving magnesium enolates have not appeared[23], although in one case chelation seems to be slightly better compared to the lithium analogue[29].

2.3. Other Organometallic Reagents

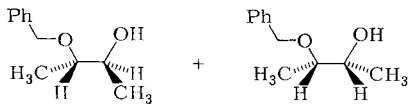
In early studies devoted to the application of organotitanium reagents to organic synthesis, we discovered that **60** undergoes chemo- and stereoselective C-C bond forming reactions with carbonyl compounds[30] and S_N1-active alkyl halides[31]. Some of these reactions depend upon the pronounced Lewis acidity of **60**. Furthermore, **60** as well as titanium tetrachloride **61** readily form octahedral complexes with two donor molecules (e.g., ether, THF) or with bidentate ligand systems[32-34]. These observations set the stage for testing Lewis-acidic titanium reagents in chelation-controlled reactions of alkoxy carbonyl compounds.

60 H_3CTiCl_3 $TiCl_4$ **61**

Addition of **60** (prepared quantitatively from dimethylzinc and $TiCl_4$ in CH_2Cl_2) to the aldehyde **48** led to **63** and **64** in the ratio 92 : 8, consistent with an intermediate of the type **62**[26].

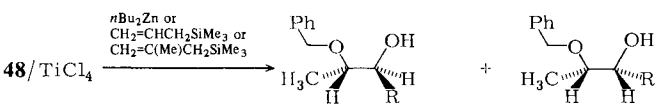


48 **62**



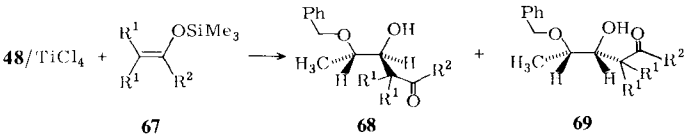
63 92 : 8 **64**

48 can also be "tied up" by $TiCl_4$ and selectively alkylated by adding mild C-nucleophiles such as dialkylzinc, allylsilanes, or allylstannanes which do not destroy chelation (e.g., **48** → **65**)[26]. For comparison, allylmagnesium chloride reacts with **48** to afford **65b** and **66b** in the ratio 60 : 40. In the addition of allylsilanes, we found the somewhat milder $SnCl_4$ to be equally well suited[35,36], as also reported by *Heathcock* et al.[37]. $TiCl_4$ and $SnCl_4$ are similar in that both are capable of forming six-coordinate octahedral complexes[34]. Interestingly, $MgBr_2$-etherate in CH_2Cl_2 (−30 °C/3 h) also promotes this reaction, but the stereoselectivity (70 : 30) and conversion (ca. 50%) are inferior[36]. One equivalent of Al_2Cl_6 ($AlCl_3$ is dimeric in solution) affords **65b** and **66b** in the ratio 85 : 15 (CH_2Cl_2/−78 °C/3 h; ca. 80% conversion)[36]. In contrast, BF_3 is incapable of chelating, and in fact causes reversal of diastereoselectivity (Section 4).



	65		**66**
a, R = *n*Bu	90	:	10
b, R = $CH_2CH{=}CH_2$	>93	:	<7
c, R = $CH_2C(Me){=}CH_2$	>95	:	<5

Silyl enol ethers **67** are also excellent C-nucleophiles[26]. This is synthetically important, because they constitute the

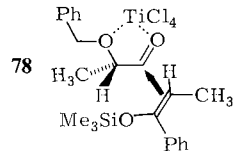


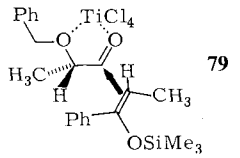
	67	68		69
a, R^1 = H, R^2 = Ph		96	:	4
b, R^1 = H, R^2 = *t*Bu		>95	:	<5
c, R^1 = CH_3, R^2 = OCH_3		>97	:	<3

only currently known class of compounds for chelation-controlled aldol additions to α-alkoxy aldehydes.

In view of this, it was of interest to determine how prochiral silyl enol ethers behave. In the reaction of the complex **48**/$TiCl_4$ with pure **70a**, *essentially only one of four possible diastereomers is formed*[26]. The X-ray structure determination of **71** shows that it is the chelation-controlled product in which simple diastereoselectivity is *syn*. Since the Mukaiyama aldol addition involving normal aldehydes is known to be non-selective[38] (e.g., **70a** reacts with propanal/$TiCl_4$ to form a 66:34 *syn/anti*-mixture[39]), this stereoselection is remarkable. **48**/$SnCl_4$ + **70a** gives the same result[26]. Activation of an aldehyde RCHO by Lewis acids is generally assumed to occur by complexation to the carbonyl group *anti* to the R group (Section 6); however, chelation necessarily involves *syn*-complexation, and this may be the determining factor for the unexpectedly high simple diastereoselectivity. This special effect was first observed in reactions of β-chiral, β-alkoxy aldehydes[39] (Section 3) and thus appears to be general. Indeed, the influence of chelation on simple diastereoselectivity is also apparent in the reaction of the *achiral* aldehyde **75**. For α-chelation, $SnCl_4$ is often more efficient than $TiCl_4$[40].

The lithium (*Z*)-enolate corresponding to **70a** shows non-chelation control (**71** : **72** : **73** : **74** = 10:60:30:0), and the zinc analogue is non-selective (11:23:50:16 ratio). Addition of preformed trichlorotitanium enolate (generated by adding $TiCl_4$ to **70a**) results in chelation control: (**71** : **72** : **73** : **74** = 89:8:3:0). In order to gain further mechanistic information, **48**/$TiCl_4$ was allowed to react with the (*E*)-isomer **70b**[40]. The product distribution 85:0:0:15 shows that complete chelation control again pertains, and that the sense of simple diastereoselectivity is *independent* of the configuration of the silyl enol ether. This suggests participation of the open-chain transition states **78** and **79**.





Although this and alternative models correctly predict chelation control, the prediction of the sense of simple diastereoselectivity is more difficult[26,40]. Not only the methyl group of the enolates **70**, but also the relative steric bulk of the other two enolate substituents exert steric influence. For example, replacing the phenyl group in **70a** by ethyl, reverses simple diastereoselectivity, i.e., the (*Z*)-silyl enol ether from 3-pentanone reacts with **48**/$TiCl_4$ with complete chelation control, but the simple diastereoselectivity is *anti* (*anti/syn* = 82:18)[36]. Furthermore, a (*Z*)/(*E*)-mixture of 66:34 leads to an *anti/syn* distribution of 56:44. The influence of different enolate substituents is also apparent in ester additions (Table 1)[36]. Included are the lithium enolates, which afford Felkin-Anh products

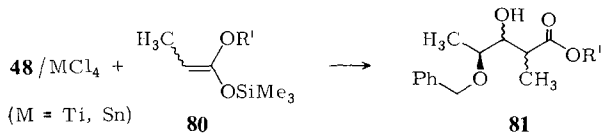
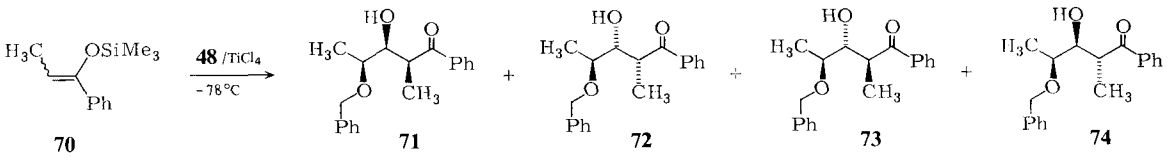


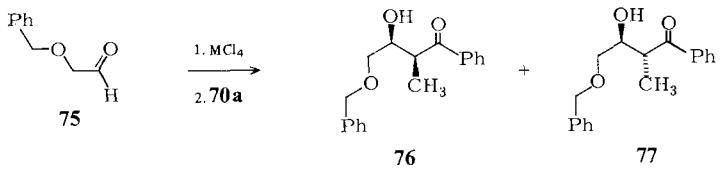
Table 1. Stereoselective formation of **81** [a].

Entry	R′	*Z* : *E*	Lewis acid	Chelation: non-chelation	Simple diastereoselectivity (*syn* : *anti*)
1	CH_3	17 : 83	$TiCl_4$	>99 : 1	23 : 77
2	CH_3	17 : 83	$SnCl_4$	>99 : 1	20 : 80
3	*t*Bu	>99 : <1	$TiCl_4$	89 : 11	65 : 35
4	*t*Bu	>99 : <1	$SnCl_4$	88 : 12	66 : 34
5	CH_3	5 : 95	—	20 : 80	69 : 31
6	CH_3	95 : 5	—	26 : 74	84 : 16
7	*t*Bu	>99 : <1	—	21 : 79	66 : 34

[a] Entries 1–4: silyl enol ether **80** and Lewis acids in CH_2Cl_2; entries 5 and 7: Li-enolates in THF; entry 6: THF/hexamethylphosphoric triamide (HMPT), all reactions at −78°C (conversion >85%).



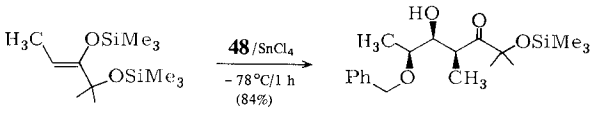
	(chelation/*syn*)		(non-chelation/*syn*)		(non-chelation/*anti*)		(chelation/*anti*)
a, Z-isomer	97	:	3	:	0	:	0
b, *E*-isomer	85	:	0	:	0	:	15



	76		**77**
$TiCl_4$	90	:	10
$SnCl_4$	95	:	5

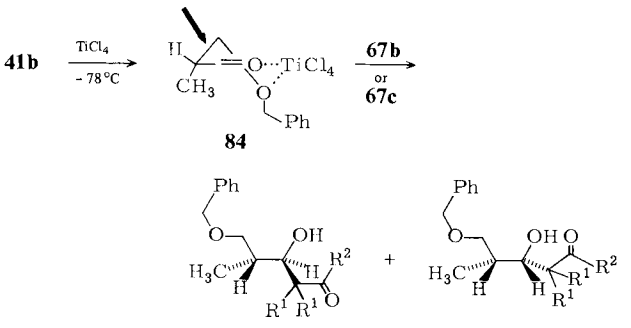
preferentially (titanium enolates are better suited, as discussed in Section 4).

An important example illustrating the usefulness of the present methodology involves the addition of silyl enol ether **82** to **48**/$SnCl_4$, which results in a single diastereomer **83**[40]. The lithium enolate affords a mixture[10], and **48**/$TiCl_4$/**82** fails to react[40].



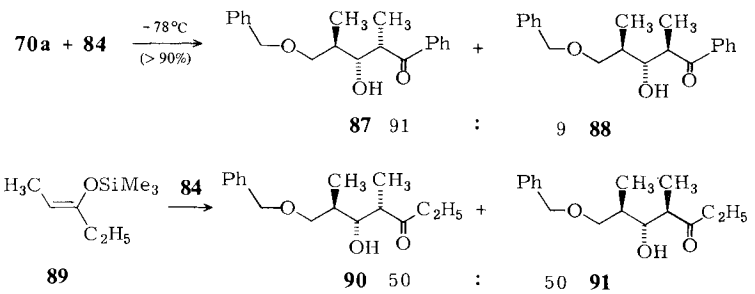
82 **83**

In the β-alkoxy series, chelation-controlled aldol additions involving **84** are also possible, e.g., by using the silyl enol ethers **67b** and **67c** from pinacolone or isobutyric acid ester[41]. Allylsilane additions are slightly less selective[35,37,41].

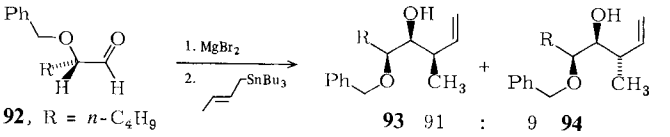


a, R^1 = H, R^2 = *t*Bu 95 : 5
b, R^1 = CH_3, R^2 = OCH_3 >97 : <3

Prochiral **70a** adds to **84** with complete chelation control, simple diastereoselectivity also being excellent (*syn* : *anti* = 91 : 9)[40]. The other two diastereomers are not formed. Again, chelation boosts simple diastereoselectivity. **89** also adds to **84** with chelation control, but not with any degree of simple diastereoselectivity[36].



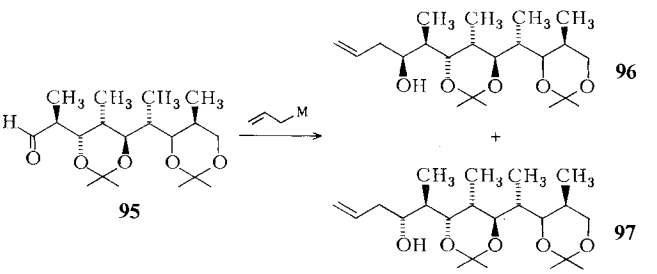
In summary, $TiCl_4$- or $SnCl_4$-induced additions of R_2Zn, silyl enol ethers, or allylsilanes to α- and β-alkoxy aldehydes have emerged as a powerful synthetic tool, and further progress involving other nucleophiles and/or more complicated aldehydes and ketones with two chiral centers is likely. In fact, allyl- and crotylstannanes add to α-alkoxy aldehydes in chelation-controlled processes mediated by Lewis acids such as $TiCl_4$, MgX_2, or ZnX_2, as recently



92, R = *n*-C_4H_9 **93** 91 : 9 **94**

shown by *Keck* et al.[42]. Since the stereochemistry of Lewis acid-mediated addition of crotylstannane to achiral aldehydes is known to be *syn*[11], good chelation control *and* simple diastereoselectivity in the reaction of **92** to **93/94** come as no surprise.

A $ZnBr_2$-mediated Grignard reaction has been reported, but its generality is unknown[43]. Allylzinc or -tin reagents (in the absence of catalysts) have not been investigated in a systematic way, but *Kishi* et al. reported interesting results for aldehydes of the type **95**[44]. Depending on its state of purity, diallylzinc reacts with **95** to afford **96** and **97** in the ratios 82 : 18 to 94 : 6. The CH_2=$CHCH_2I$/$SnCl_2$ system is



even more selective (96 : 4). A chair *trans*-decalin-type of transition state **98** is believed to be involved, in contrast to the energetically less favorable boat analogue **99** or *cis*-decalin-like conformations[44]. In **95** and in similar compounds, the relative configuration of the chiral centers is expected to influence the degree of chelation control. Such effects are indeed observed and can be rationalized[44].

With the exception of RLi and RMgX, little is known about the addition of organometallics to alkoxy *ketones*. Methylzirconium and -titanium reagents add to α-alkoxy ketones with levels of chelation control which equal or surpass analogous reactions with RMgX[45,46].

3. Chelation-Controlled 1,3- and 1,4-Asymmetric Inductions

Control of 1,3-asymmetric induction in Grignard and aldol additions to acyclic carbonyl compounds of the type **100** is not possible using reagents such as RMgX, RLi, R_2CuLi, lithium enolates, or allylboron compounds[25,39,47]. We were able to solve this problem in the same manner as in 1,2-stereocontrol, i.e. by employing Lewis-acidic titanium reagents (Section 2.3). Thus, **100** is converted into **102** with unprecedented diastereofacial selectivity[39] (Table 2). Based on these observations, it was subsequently found that $SnCl_4$ is also a useful Lewis acid for allylsilane additions[35,37].

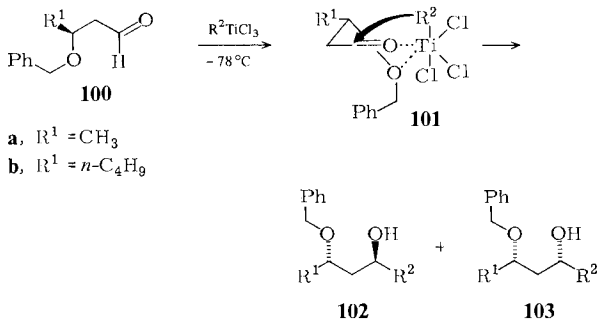
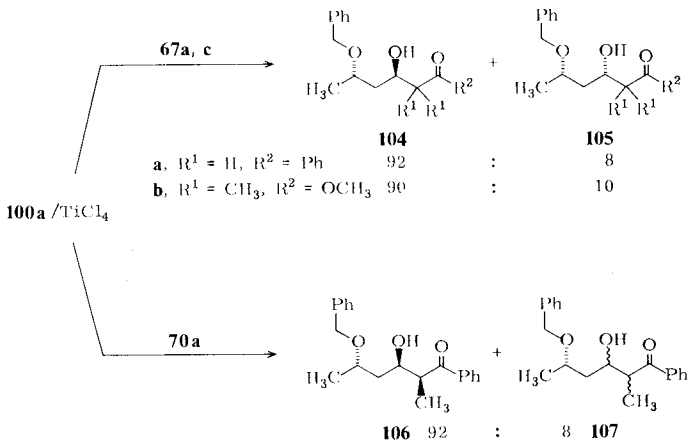


Table 2. 1,3-Asymmetric induction in addition reactions of **100** [39].

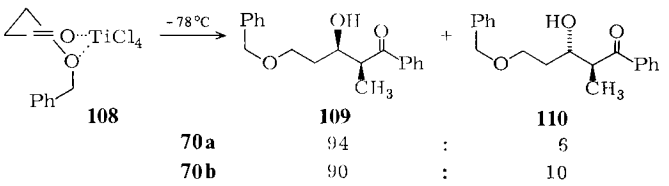
Reagent [a]	R^1	R^2	**102** : **103**
CH_3TiCl_3	CH_3	CH_3	90 : 10
$TiCl_4/CH_2{=}CHCH_2SiMe_3$	CH_3	$CH_2{=}CHCH_2$	95 : 5
$TiCl_4/CH_2{=}C(CH_3)CH_2SiMe_3$	CH_3	$CH_2{=}C(CH_3)CH_2$	95 : 5
$TiCl_4/Zn(n\text{-}C_4H_9)_2$	CH_3	$n\text{-}C_4H_9$	90 : 10
CH_3TiCl_3	$n\text{-}C_4H_9$	CH_3	91 : 9
$TiCl_4/CH_2{=}CHCH_2SiMe_3$	$n\text{-}C_4H_9$	$CH_2{=}CHCH_2$	95 : 5
$TiCl_4/CH_2{=}C(CH_3)CH_2SiMe_3$	$n\text{-}C_4H_9$	$CH_2{=}C(CH_3)CH_2$	99 : 1

[a] All reactions at −78 °C in CH_2Cl_2; for $TiCl_4$, complexation and reaction at −78 °C.

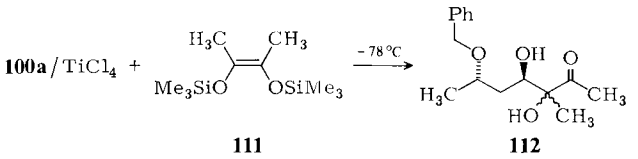
The use of silyl enol ethers facilitates 1,3-asymmetric induction in aldol reactions for the first time[39]. Remarkably, **70a** adds to **100a**/$TiCl_4$ to provide essentially only one (**106**) of four diastereomers. Simple diastereoselectivity is *syn*. **100a**/$SnCl_4$ affords three diastereomers; β-chelation is thus more effective with $TiCl_4$.



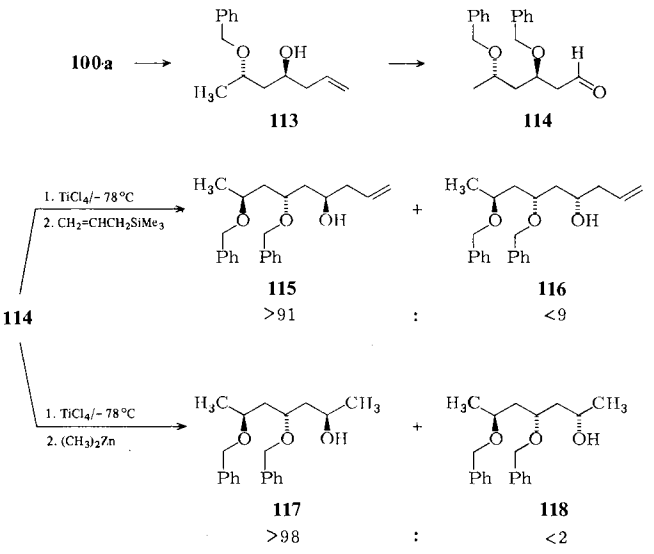
In order to explore the effect of chelation on simple diastereoselectivity, reactions of chelated achiral 3-benzyloxypropanal **108** with (*Z*)- and (*E*)-**70** were preformed. Stereoselectivity is independent of the enolate configuration. This is in accord with an "acyclic" approach of the silyl enol ether to **108** (see Section 2.3), but certainly does not prove such a mechanism.



Complete 1,3-asymmetric induction is also possible using the bis(trimethylsilyl) enol ether **111**, which adds to **100a**/$TiCl_4$ to afford only two of four possible diastereomers (>70:30). Both products are chelation controlled, but the simple diastereoselectivity has not been elucidated[36].

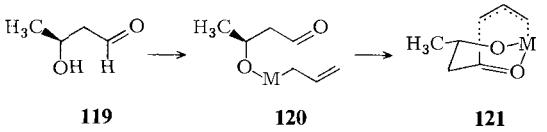


The idea that allyl- and crotylmetal reagents can be used as "masked enolates" has been developed by *Hoffmann* et al.[11,48]. We have applied this strategy to perform iterative additions. For example, the allyl adduct **113** (prepared on

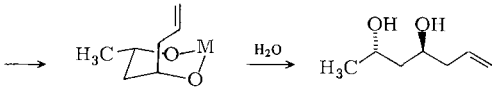


an 80 mmol scale in 92% yield and in >99% isomeric purity after one distillation) was *O*-benzylated and ozonized, and the product **114** again subjected to chelation-controlled additions (−78 °C/5 min; conversion >85%)[36]. Repetitive 1,3-stereorelations involving hydroxy groups occur in certain natural products[49].

Strategies relating to *intramolecular transfer* of C-nucleophiles, such as **119** → **123**, are beginning to be considered. **119** reacts with tetraallylzirconium to afford **123** in 81% diastereoselectivity[39].

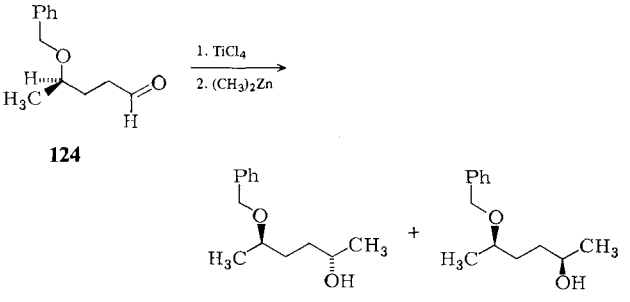


119 **120** **121**



122 **123**

Several cases of 1,4-asymmetric induction based on seven-membered chelates have been studied[26,45], e.g., **124** → **125** + **126**[26]. Allylsilane addition to **124** is 75% stereoselective[36].



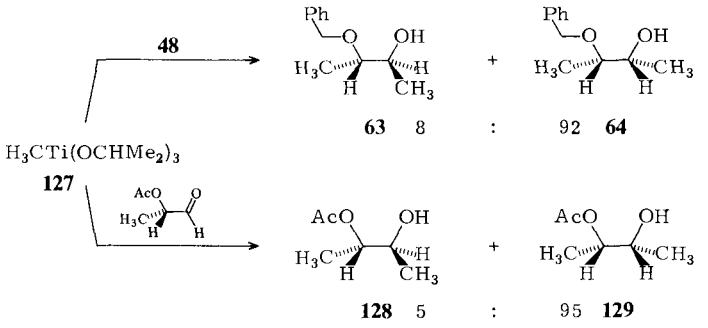
124

125 85 : 15 **126**

4. Non-Chelation-Controlled Additions

Non-chelation control is a formidable task because there is no general way to reduce the number of degrees of freedom of non-complexed molecules. Reagents incapable of chelation must be used and electronic and/or steric factors relied upon, notably those defined by the Felkin-Anh or Cornforth (dipolar) models. In fact, up till now reversal of diastereoselectivity in favor of non-chelation has only proved feasible for 1,2-asymmetric induction.

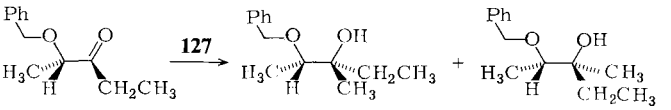
Since the Lewis acidity of alkyltitanium reagents decreases drastically in going from $RTiCl_3$ to $RTi(OR')_3$[50,51], we speculated that the latter might be *incapable* of chelation. Indeed, the complex $CH_3Ti(OCHMe_2)_3$ **127** reacts with **48** to afford preferentially the Felkin-Anh product **64** (**63** : **64** = 8 : 92)[26]. Presently, this is the only CH_3-metal compound known which permits non-chelation control. Thus, chelation or non-chelation control is possible in a predictable way simply by varying the ligands at titanium (CH_3TiCl_3 affords a 92 : 8 ratio; Section 2.3). For α-acetoxy aldehydes, stereo- and chemoselectivity is observed, as in the formation of **129**[50]. This methylation method is general and has been applied to carbohydrates (Section 5). The Felkin-Anh model (or possibly the Cornforth hypothesis) provides a satisfactory explanation.



63 8 : 92 **64**

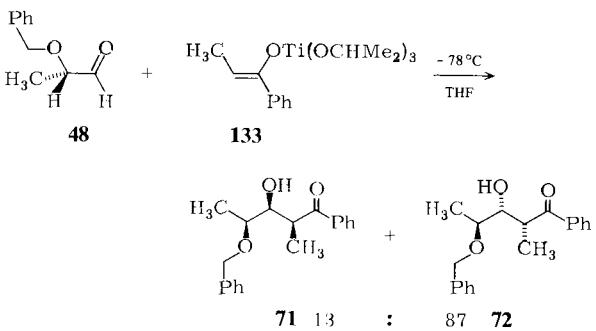
128 5 : 95 **129**

In view of these results, reaction of **127** with ketones such as **130** came as a surprise[46]. In this case the ratio of products **131** and **132** (>98 : <2) is the same as in the addition of CH_3TiCl_3 or CH_3MgCl to **130**! Either ketones are such strong Lewis bases that even **127** participates in chelation, or some other conformation is involved. Actually, theory predicts greater 1,2-asymmetric induction (Felkin-Anh-products) for ketones compared to aldehydes, because the π^*_{ketone} MO lies higher in energy than the $\pi^*_{aldehyde}$ MO, making $\pi^*_{C=O}$-σ^*_{C-X} mixing more important[52].



130 **131** >98 : <2 **132**

Titanium enolates of low Lewis-acidity react with chiral α-alkoxy aldehydes via non-chelation control[26]. A case in point is the addition of **133** to **48**, which affords only two of the four possible diastereomers[*]. This is another example of reversal of diastereoselectivity by substitution of chloro by alkoxy ligands at titanium. Simple diastereoselectivity is *syn*, as in reactions with achiral aldehydes[30,50].

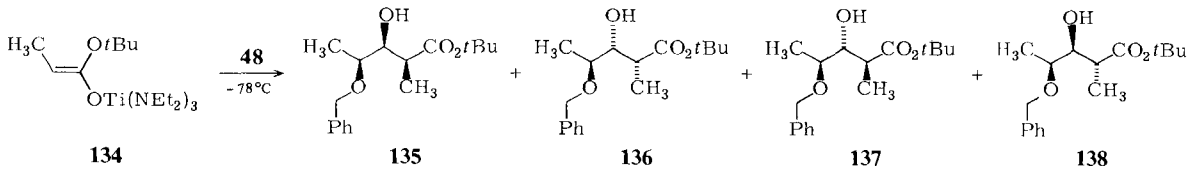


48 **133**

71 13 : 87 **72**

Sometimes tris(diethylamino)titanium enolates are better suited. With **134**, 93% non-chelation control and >90% simple diastereoselectivity are observed[36]. The corresponding Li-enolate affords all four diastereomers (Table 1), as does the triisopropoxytitanium analogue (**135** : **136** : **137** : **138** = 14 : 33 : 35 : 18)[36]. Other Li-enolates show modest levels of non-chelation control[10]. In these

[*] The configurational assignment with regard to simple diastereoselectivity in the formation of the major isomer **72** has now been ascertained by chemical correlation [41].



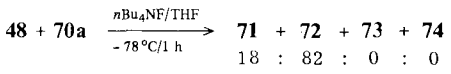
134 **135** **136** **137** **138**

(chelation/*syn*) (non-chelation/*syn*) (non-chelation/*anti*) (chelation/*anti*)

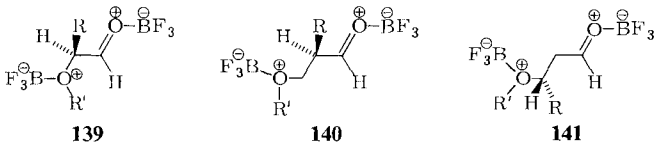
7 : 85 : 8 : 0

cases, *Heathcock* et al. have performed elegant experiments involving optically active enolates in order to increase diastereofacial selectivity[53]. The principle of double stereodifferentiation seems promising in this area.

A different approach to non-chelation control involves ammonium enolates. Using Noyori's method of fluoride ion induced aldol additions[54], we allowed **48** to react with **70a** under conditions of kinetic control and observed only two of the four diastereomers with 82% non-chelation control and 100% simple diastereoselectivity (*syn*)[41]. It remains to be seen to what extent this method can be generalized.



A third strategy makes use of Lewis acids which are incapable of chelation. By using two equivalents of gaseous BF_3, double complexation of **11**, **13**, and **15** might be expected to result in formation of adducts **139**, **140**, and **141** with rigid conformations due to electrostatic repulsion[41]. Nucleophilic attack from the less hindered side in **141** simulates chelation control, and this has been verified experimentally[35]. In contrast, **139** and **140** are expected to form products of non-chelation control.

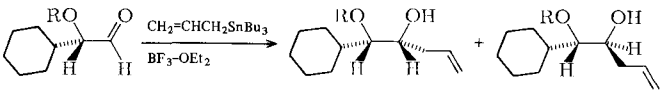


139 **140** **141**

R = CH_3, R' = CH_2Ph

Indeed, addition of allyltrimethylsilane or the silyl enol ethers **67b** and **67c** to **139** (−95°C/1 h) results in significant levels of non-chelation control (**65b** : **66b** = 20 : 80, **68b** : **69b** = 10 : 90 and **68c** : **69c** = 16 : 84)[41]. Addition of **67b** to **140** results in a product distribution **85a** : **86b** = 12 : 88, which is again synonymous with non-chelation control[41]. $BF_3 \cdot Et_2O$ is considerably less efficient. Besides the "Cornforth conformations", **139** and **140**, the results are also consistent with Anh's theory[41].

Keck et al. have shown that allylstannanes also undergo BF_3-mediated non-chelation-controlled additions[42]. For the bulky aldehyde **142**, the *tert*-butyldimethylsilyl protecting group results in higher selectivity than the benzyl group. However, useful stereoselectivity is not observed with other α-alkoxy or α-siloxy aldehydes (e.g., α-siloxy pentanal). For α-chiral, β-siloxy aldehydes, reaction with crotylstannanes results in excellent non-chelation control and simple diastereoselectivity (*syn*)[42].



142 **143** **144**

a, R = CH_2Ph 61 : 39

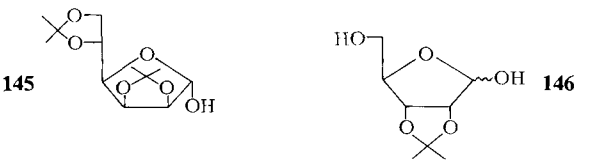
b, R = $SitBuMe_2$ >91 : <9

Although allylboron compounds might be expected to exhibit non-chelation control, selectivity in the reaction of α-benzyloxy propanal **48** with 2-allyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane is meager (**65b** : **66b** = 35 : 65)[55]. However, in sugar chemistry, aldehydes react very selectively with certain allylboron compounds (Section 5).

Finally, several special cases of non-chelation control in the addition of Li- and Mg-enolates to certain α-chiral, β-alkoxy (or siloxy) aldehydes have been reported. These include key steps in the synthesis of erythromycin A by *Woodward* et al.[56], maytansinoids by *Meyers* et al.[57], and monensin by *Still* et al.[23]. Nevertheless, there are not enough data to draw up general guidelines for enolate reactions of this type[10]. For non-chelation, Cram's rule may be applied.

5. Addition Reactions in Carbohydrate Chemistry

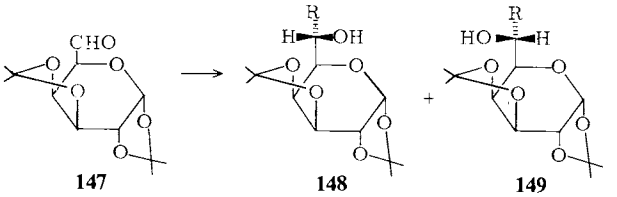
Although some of the general points mentioned in this article also apply to carbohydrate aldehydes and ketones, additional factors often have to be considered. Surprises and mechanistic uncertainties prevail in a number of situations. For example, Grignard additions to the mannofuranose **145** follow different stereochemical pathways, depending upon whether EtMgBr or HC≡CMgBr is used[58]. In contrast, **146** reacts with benzylmagnesium chloride to provide a single diastereomer having the D-*allo*-configuration[59].



145 **146**

In other cases, interpretation of the stereoselectivity using *Cram*'s cyclic model is straightforward. For example, several groups[60,61] have described chelation-controlled

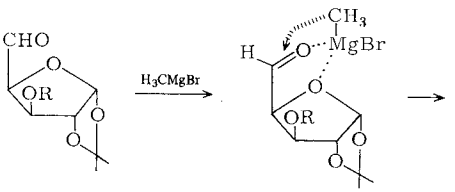
Grignard additions to D-galactose derivatives (e.g. **147**)[61]. According to *Schöllkopf*, α-chelation with the oxygen atoms of the carbonyl group and the pyran ring determines the sense of diastereofacial selectivity[61].



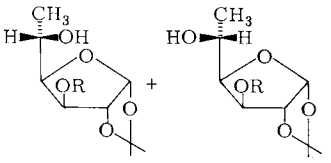
147 **148** **149**

H_3CMgBr	80	:	20
	>98	:	<2

Similarly, *Hanessian* et al.[62a] and *Inch*[62b] postulate chelation of the type shown in **151** to explain the preferred formation of **152** in the Grignard addition to **150**[62]. Coordination with the less basic β-benzyloxy group cannot compete effectively. In order to "turn off" chelation and thus to reverse diastereofacial selectivity, we performed the reaction with $CH_3Ti(OCHMe_2)_3$[26]. Exclusive formation of the Felkin-Anh product **153** is in accord with the non-chelation control observed with other aldehydes (Section 4), and documents the synthetic value of this methodology[26,50].



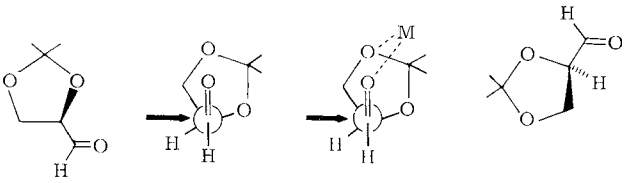
150, R = CH_2Ph **151**



	152		**153**
H_3CMgBr	88	:	12
$H_3CTi(OCHMe_2)_3$	<1	:	>99

2,3-*O*-Isopropylidene-D-glyceraldehyde **154** or its enantiomer as well as similar compounds have been allowed to react with a large number of Grignard reagents and enolates. Up to about 1980, most of the reactions reported were fairly unselective[10,63]. Since then enormous progress has been made by careful choice of reagents and conditions. These reactions are often the starting point of natural products syntheses. The diastereofacial selectivity of the reactions is *anti* (Masamune nomenclature)[*] and has generally been explained by the Felkin-Anh model **155**

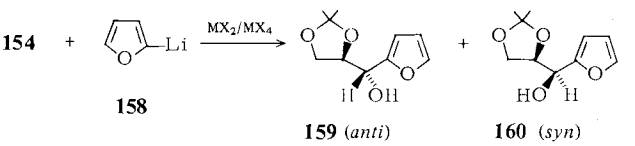
[*] The *syn/anti*-nomenclature is used both for the diastereofacial selectivity and for simple diastereoselectivity [1c].



154 **155** **156** **157**

without any complexation to the α- or β-oxygen. β-Chelation **156** has also been postulated and leads to a synergistic effect (type **19**). However, a Cornforth-type of conformation **157** also accommodates the data.

Mukaiyama et al. have published a series of papers in this area[64]. For example, in their synthesis of D-ribulose, addition to **154** constitutes the key step[65]. Table 3 shows that ZnX_2-mediated reactions are best. Although the nature of the actual reacting organometallic species is not known, **156** (M = Zn) was postulated.



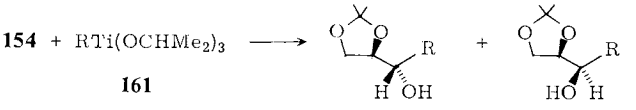
158 **159** (*anti*) **160** (*syn*)

Table 3. Stereoselective reaction of **154** to **159**/**160**.

MX_2/MX_4 [a]	*T* [°C]	Yield [%]	**159** : **160**
—	−78	68	40 : 60
$MgBr_2$	0	49	50 : 50
$SnCl_4$	0	58	95 : 5
$ZnCl_2$	0	60	90 : 10
$ZnBr_2$	0	75	95 : 5
ZnI_2	0	57	95 : 5

[a] All reactions in THF, except the $SnCl_4$-mediated addition (toluene).

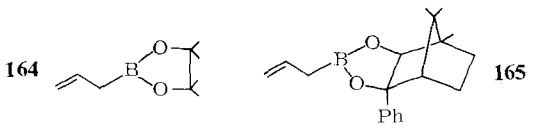
The stereoselective introduction of methyl groups into **154** is very difficult[63]. We therefore employed $CH_3Ti(OCHMe_2)_3$ in the hope of effecting non-chelation control. The ratio of *anti*:*syn*-adducts was in fact 75:25 (THF/−78 °C/5 h; >85% conversion)[66], which is not exceedingly good, but better than in previous methods[63]. *Mulzer* et al. have used organotitanium reagents to add other groups[67]. Oddly, the phenyltitanium reagent **161d** favors the *syn*-adduct **163d**, which is a rare exception in nucleophilic additions to **154**. *Mulzer* et al. have also studied other organometallic reagents (Li, Mg, Zn, and Cr) and discuss various models, including tridentate chelation involving the aldehyde function and both alkoxy groups[67].



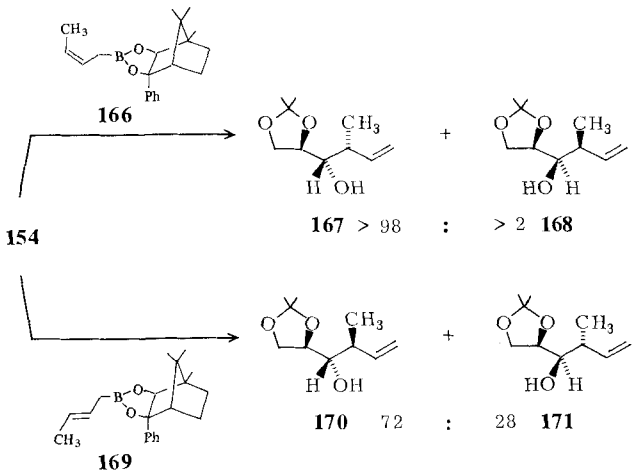
161 **162** **163**

a, R = CH_3	75	:	25
b, R = *n*Bu	90	:	10
c, R = CH_2=$CHCH_2$	71	:	29
d, R = Ph	9	:	91

Considerable effort has gone into adding allyl groups to **154**. Although diallylzinc affords a 91:9 ratio of **162c** : **163c**[67], a better result is reached using boron reagents. *Hoffmann* et al. have shown that switching from **164** to optically active **165** increases the **162c** : **163c** ratio from 80:20 to 96:4[68].

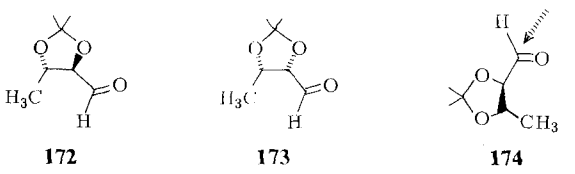


The optically active crotylboron reagents **166** and **169** have also been tested[68]. The former delivers one (**167**) of four diastereomers, the latter a mixture of **170** and **171**. Whereas simple diastereoselectivity depends in a predictable way on the configuration of the crotyl double bond[11,48], the phenomenon behind the different degrees of diastereofacial selectivity is not easily pinpointed. With racemic **169**, the **170** : **171** ratio dropped to 67:33, which shows that double stereodifferentiation is involved. Preliminary reactions involving other aldehydes indicate that the Anh model is *not* necessarily the optimal explanation[69]. Perhaps the reactions of allylboron compounds can be viewed as cycloadditions in which there is little flow of electron density from the reagent to the aldehyde[69].

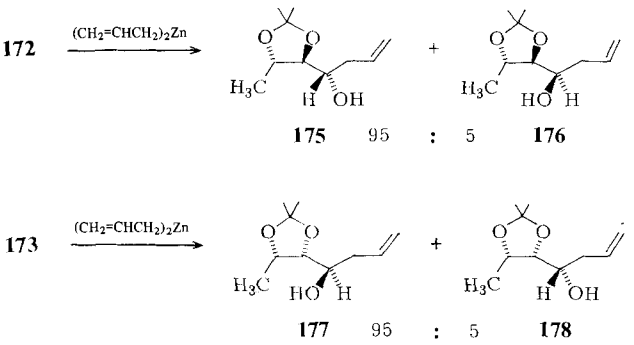


154 has also been used in other stereoselective additions[70]. Certain enolates are *anti*-selective to a greater or lesser extent[10,53]. Electrochemically generated dichloroacetate enolates add very selectively, as described by *Shono* et al.[71]. In all cases the Felkin-Anh model **155** was invoked to explain the stereoselectivity.

anti-Stereochemistry is also generally observed for β-substituted substrates of the type **172** and **173**. For the *trans*-isomer **172**, the same phenomena should operate as in **154**. The *cis*-compound **173** is different, because transition states of the type **155** or **156** would involve unfavorable steric interactions between the incoming nucleophile and the methyl group, an aspect which has not been discussed in the literature. It seems that a Cornforth-type of conformation **174** is a more plausible explanation for the observed *anti*-selectivity.



Fuganti et al. have reported many elegant additions of diallylzinc or propargylzinc reagents to **172** and **173** as well as to imine analogues[72]. The stereoselective formation of **175** and **177** are typical examples.

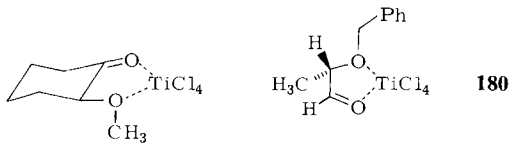


This method has been used for the synthesis of various natural products. An outstanding example is the synthesis of the amino sugars L-daunosamine and L-ristosamine from the phenylsulfenimines derived from **172** and **173**, respectively[73]. *Roush* et al. used allylboron compounds[11] to synthesize D-fucose derivatives[74]. An exception to the general rule regarding *anti*-stereoselection has recently been published, but not explained[75]. Also, *ketones* related to **154** react with RMgX to form preferentially *syn*-adducts[76]. Perhaps this involves chelation of the more basic ketone oxygen and the α-alkoxy group.

Finally, a number of related processes have been reported. These include hetero-Diels-Alder reactions of **154** as described by *Danishefsky* et al.[77]. Furthermore, Wittig reactions of **154** yield olefins, which have been used in stereoselective Diels-Alder reactions[78], 1,3-dipolar cycloadditions[79], cyclopropanation induced by phosphorus ylides[80], as well as Michael additions[81]. The observed 1,2-asymmetric induction can be explained on the basis of the Houk-model[82], which has some similarity to the Anh-theory.

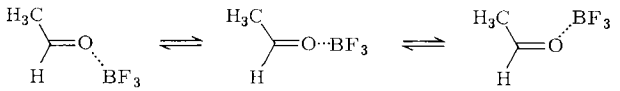
6. Mechanistic Studies

Despite the synthetic progress in chelation and non-chelation control, shortcomings persist in terms of the mechanism. For example, the products of chelation control are usually rationalized solely on the basis of the stereochemical outcome. Until recently, no direct physical evidence for intermediate chelates had been presented. Although X-ray structural data on such species have not yet been completed, ^{1}H- and ^{13}C-NMR spectroscopic studies have been performed[26,66]. Thus, the NMR data for **179** (which reacts 100% stereoselectively with allylsilanes)[26] and **180** are consistent with the proposed structures.



179 **180**

Although a host of Lewis acid adducts with carbonyl compounds are known[34], no X-ray crystallographic data on ketone or aldehyde complexes are available[83]. Since the question of *syn*- or *anti*-complexation of aldehydes is of mechanistic importance, *Rademacher* et al. performed some MNDO calculations on the BF_3-adduct of acetaldehyde[84]. The difference in energy between the *anti*- (**181**) and *syn*-adduct (**183**) is only ca. 2 kcal/mol. The linear form **182** shows no minimum, but π-coordination has not yet been explored. Recently, *Helmchen* came upon the latter phenomenon in an X-ray crystallographic study of a $TiCl_4$-diester adduct[85]. Clearly, more work is necessary before details of mechanistic hypotheses become meaningful.



181 **182** **183**

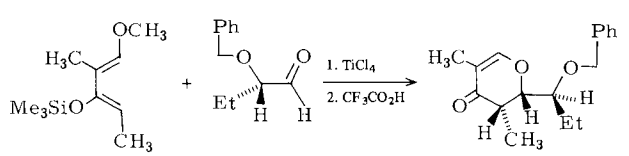
- 297.07 - 291.79 - 295.27

ΔH_f [kcal/mol]

7. Conclusions and Addendum

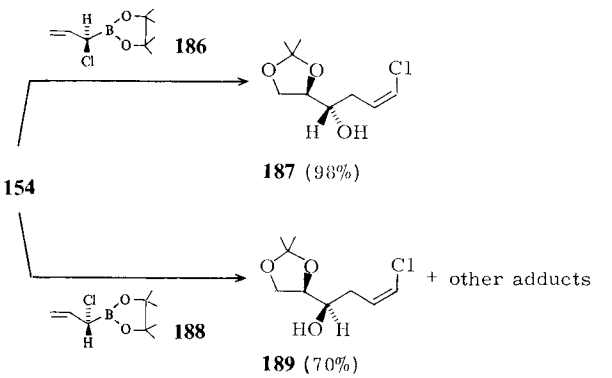
A variety of reliable methods for chelation control in nucleophilic additions to chiral α- and β-alkoxy carbonyl compounds are available. Further elaborations are certain to follow, including the use of synthetically useful C-nucleophiles not previously tested. A more difficult task is the development of new and better ways of non-chelation control. As far as predictive guidelines for the latter are concerned, any one of the qualitative models (Felkin, Anh, or Cornforth) may be used. It is a challenge to devise experiments which illuminate the real mechanism in a given case.

Since the submission of this manuscript, further progress has been made. A steroidal α-alkoxy aldehyde has been allowed to react with a lithium dienolate under conditions of chelation control, and the aldol adduct converted into withanolide D[86]. In an extension of their work on cyclocondensations of aldehydes with dienes of the type **184**, *Danishefsky* et al. have reported chelation-directed asymmetric C–C-bond forming reactions, e.g. the synthesis of **185**[87].



184 **38** **185**

Finally, *Hoffmann* et al. have carried out reactions based on the principle of double stereodifferentiation[69]. Whereas the optically active allyl boronate **186** reacts with **154** to form the *anti*-adduct **187**, diastereofacial selectivity is reversed if the enantiomer **188** is employed!



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Microbial Asymmetric Catalysis—Enantioselective Reduction of Ketones

New Synthetic Methods (45)

By Charles J. Sih* and Ching-Shih Chen

Microbial asymmetric reduction of ketones is a method widely used for the preparation of chiral alcohols. The present progress report deals with the basic concepts that govern enantioselectivity of enzymes and intact cells. Strategies to control the stereochemical course of microbial reductions of carbonyl compounds and the relationship of substrate structure to enantioselectivity are considered.

1. Introduction

The asymmetric reduction of carbonyl compounds by microorganisms, a method outside the traditional arena of chemical synthesis, is now well-recognized as an invaluable tool for the preparation of chiral alcohols. Because a single microorganism contains a number of oxidoreductases, it can mediate the reduction of a variety of artificial ketones to produce chiral alcohols of remarkable optical purity. Hence, in recent years reductions of this type have been used for the introduction of the key chiral centers in target molecules in numerous total syntheses[1]. In contrast, enantioselective reduction of ketones using "chemical" catalysts (e.g., organometallic compounds) has not been widely applied to asymmetric syntheses[2]. This is because of the difficulties associated with the design of such catalysts, which is still largely empirical and requires much chemical intuition.

In this article, the underlying principles of enantioselection for isolated enzyme systems and for intact cells will be addressed first, since the dependence of rates and enantioselectivities on structural features of substrates is based on a mechanistic understanding of these concepts. Also, this background facilitates the subsequent coverage of the examples on microbial enantioselective reduction of achiral ketones. This brief overview should provide the synthetic chemist with a useful guide for the application of this simple but powerful technique, now central to modern synthetic organic methodology.

2. Theory

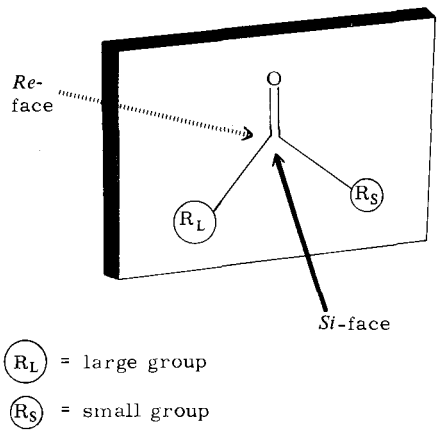
Although the present state of knowledge concerning asymmetric catalysis does not allow the prediction of the sense of chirality and the extent of asymmetric induction for a given substrate, there are certain important mechanistic concepts contributing to the process of enantioselection that merit attention. In general, asymmetric catalysis occurs because the chiral catalyst (enzyme) and prochiral substrate form diastereomeric transition states which differ in energy; the magnitude of their energy difference, $\Delta\Delta G^{\neq}$, determines the enantiomeric excess *ee*[3]. Unfortunately, this simplification has deterred many chemists from gaining a detailed understanding of the kinetic laws governing asymmetric induction. In the following, we shall attempt to discuss the origin of enantioselectivity using enzymic, enantioface discrimination as an example, but the same principles can be applied to asymmetric catalysis in general (enzymic and non-enzymic).

2.1. Isolated Enzyme Systems

Consider a prochiral ketone with enantiotopic faces *Re* and *Si*, and which is reduced to a chiral alcohol. Complexation of the chiral catalyst, the enzyme, on the *Re*-face leads to one enantiomer, whereas the other enantiomer is formed with the same probability through complexation on the *Si*-face. If the enzyme is unable to discriminate between the two faces, the resulting alcohol will be obtained as a racemate. High enantioselectivity is achieved only when the enzyme is capable of discriminating between the two enantiotopic faces. The enantioselectivity is generally expressed by the enantiomeric excess *ee*,

$$ee = ([R]-[S])/([R]+[S])$$

where $[R]$ and $[S]$ are the amounts of the enantiomers.



The reduction of a prochiral ketone by an isolated oxidoreductase generally requires the presence of either NADH or NADPH[4] as cofactors; these molecules furnish the reducing equivalents in the reaction. With the assumption that this reaction proceeds via an ordered mechanism and that NADH is used as the coenzyme, the en-

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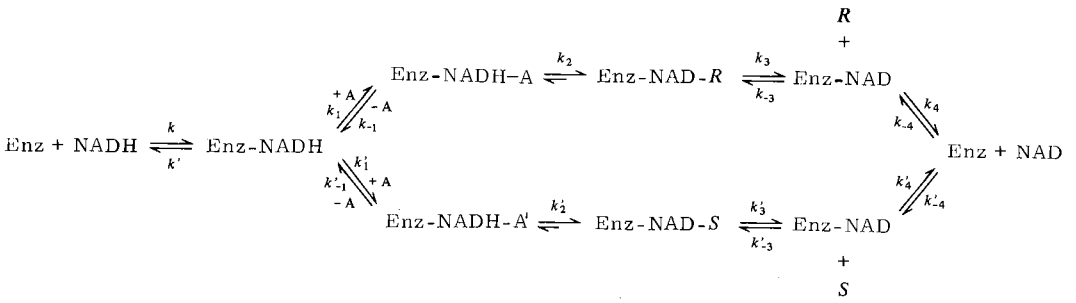
zyme first forms the complex Enz-NADH. Subsequently, the prochiral ketone A then binds to this complex either from the *Re*- or the *Si*-face with equal probability ($k_1 = k'_1$) to generate two ternary complexes (Scheme 1); the two complexes are held together with different degrees of tightness ($k_{-1} \neq k'_{-1}$). These complexes then undergo catalytic reduction to yield the (*S*)- and (*R*)-enantiomers, which are still bound to the enzyme-cofactor complex (Scheme 1).

$$RT\ln\frac{\left(\frac{k_{cat}}{K}\right)_1}{\left(\frac{k_{cat}}{K}\right)_2} = -(\Delta G^{\neq}_{T_1} - \Delta G^{\neq}_{T_2}) = -\Delta\Delta G^{\neq} \quad \text{(e)}$$

$$E' = \frac{\left(\frac{k_{cat}}{K}\right)_1}{\left(\frac{k_{cat}}{K}\right)_2} = \exp\left(-\frac{\Delta\Delta G^{\neq}}{RT}\right) \quad \text{(f)}$$



Scheme 1. Reaction mechanism for enzyme-catalyzed reductions.

Whereas Scheme 1 contains multi-step reactions, for enantioselection only those steps leading up to and including the first irreversible step (k_{cat}/K) are important. k_{cat}/K is the rate constant for the reaction of enzyme and substrate A at infinitely low substrate concentration ([A]→0). Thus, the enantioselectivity, E', of the system in Scheme 1 is dependent on the ratio k_{cat}/K [eq. (a)].

$$E' = \frac{\left(\frac{k_{cat}}{K}\right)_A}{\left(\frac{k_{cat}}{K}\right)_{A'}} = \frac{\frac{k_1}{1+C_r}}{\frac{k'_1}{1+C'_r}} \quad \text{(a)}$$

$C_r = k_{-1}/k_2$ and $C'_r = k'_{-1}/k'_2$.

According to the transition state theory[5], the equilibrium constant for the equilibrium between the transition state EnzA$^{\neq}$ and Enz+A is proportional to $\Delta G^{\neq}_T$, which is related to $\Delta G^{\neq}$, the activation energy of the bond-forming and -breaking steps, and ΔG_C, the (negative) complexation energy [eq. (b)].

$$\Delta G^{\neq}_T = \Delta G^{\neq} + \Delta G_C \quad \text{(b)}$$

These interrelationships are depicted in the energy-profile diagram (Fig. 1).

It can be shown that the kinetic constant, k_{cat}/K, is related to the thermodynamic term, $\Delta G^{\neq}_T$[6], as shown in equation (c).

$$RT\ln\left(\frac{k_{cat}}{K}\right)_1 = RT\ln\left(\frac{kT}{h}\right) - \Delta G^{\neq}_{T_1} \quad \text{(c)}$$

$$RT\ln\left(\frac{k_{cat}}{K}\right)_2 = RT\ln\left(\frac{kT}{h}\right) - \Delta G^{\neq}_{T_2} \quad \text{(d)}$$

k is the Boltzmann constant and h is Planck's constant. Subtracting equation (d) from equation (c), one obtains equation (e), which may be rearranged to yield equations (f) and (g).

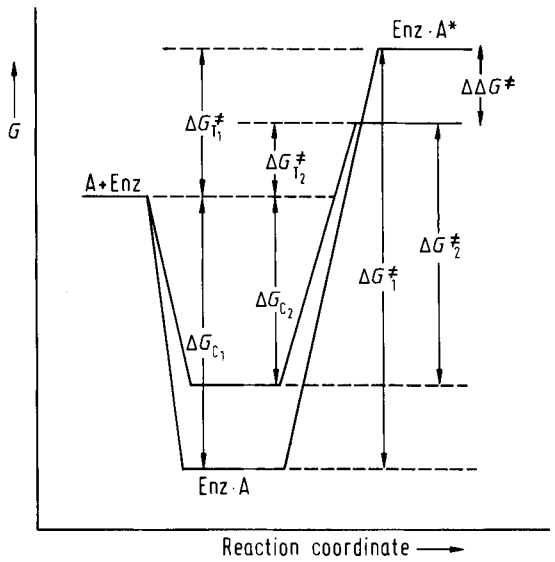


Fig. 1. Energy profile of a hypothetical enantioselective reaction.

$$\Delta\Delta G^{\neq} = -RT\ln E' \quad \text{(g)}$$

The dependence of E' and $\Delta\Delta G^{\neq}$ on the rate constants (barrier heights) of the competing reactions is shown in Table 1. These simulations provide a useful overview of the quantitative correlation between changes in the magnitude of each rate constant with the value of E'.

2.1.1. *High Enantioselection*

When the substrate (A and A') undergoes rapid and reversible exchange with Enz-NADH ($k_2 \ll k_{-1}$, $k'_2 \ll k'_{-1}$ (C_r and $C'_r \gg 1$), equation (a) simplifies to equation (h).

$$E' = \frac{k_1 C'_r}{k'_1 C_r} = \frac{C'_r}{C_r} \quad \text{(h)}$$

Table 1. Dependence of enantioselectivity E' and $\Delta\Delta G^{+}$ on the rate constants of two competing reactions (assumption: $k_1 = k'_1 = 10^6$).

No.	k_{-1}	k_2	k'_{-1}	k'_2	C_r	C'_r	E'	$-\Delta\Delta G^{+}$ (25 °C) [cal/mol]
1	0.01	100	0.01	10	0.0001	0.001	1.00	—
2	0.1	100	0.1	10	0.001	0.01	1.01	5
3	10	100	10	10	0.1	1	1.81	354
4	100	100	100	10	1	10	5.50	1010
5	100	10	100	1	10	100	9.18	1313
6	10	1	100	1	10	100	9.18	1313
7	1000	100	10	0.1	10	100	9.18	1313
8	100	1	100	0.1	100	1000	9.91	1358
9	100	1	1000	0.1	100	10000	99.0	2721
10	100	10	1000	0.1	10	10000	909.0	4034

The second-order rate constants k_1 lie typically in the range 10^6 to 10^8 M^{-1} s^{-1} for low molecular weight substrates[7]; these values are close to those for diffusion-controlled processes. Hence, the tightness of substrate binding is determined in most cases by the values of k_{-1}. Since the complexation of Enz-NADH with either A or A′ occurs with the same probability ($k_1 \simeq k'_1$), the enantioselectivity, E', is mainly dependent on the ratio of the reverse commitment to catalysis, C_r/C'_r. High enantioselection is achieved only when there is a rapid interconversion of the diastereomeric enzyme-ketone-coenzyme complexes compared with the rates of the subsequent catalytic step. The examples Nos. 1 and 4 in Table 1 illustrate this. While changes in either k'_{-1} or k'_2 alter the value of E', it is noteworthy that commitment to catalysis (C_r) is independent of the energy levels of the enzyme-substrate complex. In other words, when k'_{-1} and k'_2 are changed, but not their ratio (C'_r), the value of E' remains the same (Nos. 6 and 7 in Table 1).

2.1.2. *Poor Enantioselection*

When the substrate (A and A′) binds tightly to the enzyme complex, Enz-NADH ($k_2 \gg k_{-1}$; $k'_2 \gg k'_{-1}$; C_r and $C'_r \ll 1$), equation (a) simplifies to equation (i).

$$E' = \frac{k_1}{k'_1} \qquad \text{(i)}$$

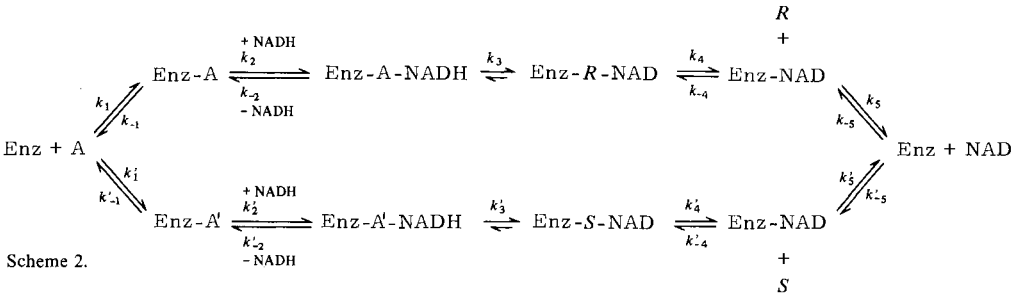
The enantioselectivity, E', is therefore now dependent on the ratio k_1/k'_1. Intuitively, this condition may be conceived as follows: during the first catalytic cycle, free enzyme proceeds through the upper and lower pathways (Scheme 1) to produce equal amounts of Enz-NADH-A and Enz-NADH-A′. Because $k_2 > k'_2$, more enzyme will proceed through the upper pathway than the lower to regenerate free enzyme. In each of the successive catalytic cycles, some Enz-NADH-A′ remains from the previous cycles (held back by slower k'_2) and continues to increase until the reaction attains a steady state, at which time

$$[\text{Enz-NADH-A}]k_2 = [\text{Enz-NADH-A}']k'_2$$

Hence the relative flow through the upper and lower pathways will be the same if $k_1 = k'_1$[8], because of the compensatory shift of the enzyme complexes in the steady state. In this situation, poor enantioselection results (Nos. 1 and 2 in Table 1).

For most oxidoreductases[9], the larger NAD(P)H does indeed bind first to the enzyme followed by the smaller ketone substrate. In these instances, enantioselectivity is independent of NAD(P)H and ketone concentrations. This treatment also holds for those oxidoreductases which obey the Theorell-Chance mechanism[10].

As the size of the artificial ketone increases, it may bind to the enzyme more tightly, and the mechanism could shift from ordered to random[11], as reported for some alternative substrates with the enzyme yeast alcohol dehydrogenase. For illustrative purposes, let us discuss what happens when the enzyme combines first with the prochiral ketone A and then with NADH (Scheme 2).



Scheme 2.

High enantioselection is attained only when there is rapid equilibration of the enzyme complexes

$$\text{Enz-A-NADH} \rightleftharpoons \text{Enz-A'-NADH}$$

In this case, the enantioselectivity, E', is related to the kinetic rate constants by equation (j).

$$E' = \frac{\left(\frac{k_{cat}}{K}\right)_A}{\left(\frac{k_{cat}}{K}\right)_{A'}} = \frac{\frac{k_1}{k_{-1}R + [\text{NADH}]}}{\frac{k'_1}{k'_{-1}R' + [\text{NADH}]}} \qquad \text{(j)}$$

where $R = \frac{k_{-2} + k_3}{k_2 k_3}$ and $R' = \frac{k'_{-2} + k'_3}{k'_2 k'_3}$

When the concentration of NADH is very low, equation (j) simplifies to equation (k), and E' is not affected by the low concentration of NADH.

$$E' = \frac{k_1 k'_{-1} R'}{k'_1 k_{-1} R} \qquad \text{(k)}$$

However, it should be noted that enantioselection decreases as the concentration of NADH is increased, since this reduces the reverse commitment to catalysis (C_r and C_r'); equation (j) then simplifies to equation (i). Enantioselectivity is not affected by the concentration of the prochiral ketone, but the concentration of NADH should be kept relatively low in preparative enzymic enantioselective reductions, especially when the artificial substrate can compete in size or binding affinity with NADH.

2.2. Intact Cells

One major complication in using intact cells for the catalytic reduction of ketones is that the process is often only partially enantioselective. This can be interpreted in two ways. 1) The ketone may be reduced by a single oxidoreductase which interacts with both faces of the carbonyl group to form two diastereomeric transition states, one of which is more favored than the other. 2) Two or more competing oxidoreductases in intact cells may generate alcohols of opposite configuration at different rates (depending on v_{max} and K). These two possibilities may be readily distinguished from each other by conducting the reduction at different substrate concentrations. In case 1), the enantioselectivity is independent of changes in substrate concentrations, whereas in case 2) it is not[12]. In our experience, virtually all partial enantioselective reductions emanate from the combined action of competing enzymes of opposite chirality in intact cells.

Despite the many enantioselective microbial reductions of ketones that have been reported, in most instances the enzyme(s) responsible for the catalytic reduction has (have) not yet been identified. Consequently, at present it is not possible to predict the configuration or the extent of asymmetric induction with any degree of confidence. Although there are a number of possible approaches to directing the stereochemical course of microbial reductions of carbonyl compounds, the one most suited to the synthetic chemist is to design substrates whose kinetic constants (apparent v_{max} and K (Michaelis constant)) for the competing oxidoreductases are considerably different. In theory, by making strategic changes in the structural features of substrate molecules, it may be possible to prepare optically pure alcohols of either configuration.

In the enantioselective reduction of ketones by two or more competing enzymes of intact cells, the three variables of interest to the synthetic chemist are A_0, the initial substrate concentration; C, the extent of conversion; and *ee*, the enantiomeric excess of the product alcohol. These key parameters are of course related to the apparent kinetic constants (v_{max} and K) of the competing enzymes. Although several methods are available for the determination of v_{max} and K of mixed enzyme systems in crude cell extracts, these apparent kinetic constants do not take into account additional variables: the number, relative concentration, and compartmentalization of competing enzymes; effective coenzyme concentration; permeability factors, etc. Hence, the apparent K and v_{max} values thus secured do not apply to intact cells.

Because of the difficulty of acquiring accurate initial rate measurements using intact cells at low substrate concentrations, especially for substrates which are not miscible with water, a time-independent method was developed to estimate the apparent kinetic constants (K and v_{max}) of intact cell systems.

The relationship of the three parameters, *ee*, A_0, and C to the apparent kinetic constants v_{max} and K is given by equation (l)

$$ee = 1 - 2\frac{A_0 C + (K_R - x)\ln\dfrac{A_0 + x}{A_0(1-C)+x}}{(1+y)A_0 C} \qquad (l)$$

where $x = \dfrac{yK_S + K_R}{1+y}$ and $y = \dfrac{v_{max(R)}}{v_{max(S)}}$

and $v_{max(R)}$, $v_{max(S)}$ and K_R, K_S denote maximal velocities and Michaelis constants for *R*-enzyme(s) and (*S*)-enzyme(s), respectively.

Two assumptions were made in the derivation of equation (l)[13]: the reaction is virtually irreversible and no product inhibition occurs. Both of these criteria are met since microbial reduction of ketones is generally irreversible when sufficient amounts of reducing equivalents are available, as is the case when the incubation mixture contains an exogenous source of either sucrose or glucose. Secondly, no product inhibition is observed until very late stages of the reaction.

Thus, by experimentally determining the values of *ee* and C at several initial concentrations A_0, the three unknowns, y, K_R, and x may be solved by numerical analyses using equation (l). This then allows one to obtain two useful dimensionless constants

$$z = [(v_{max(R)}/K_R)/(v_{max(S)}/K_S)] \quad \text{and} \quad y = v_{max(R)}/v_{max(S)}$$

which dictate the stereochemical course of the reduction; z is the ratio of the apparent first-order rate constants for the binding of substrate to the enzyme when $A_0 \ll K_R$ and K_S, and y is a measure of the ratio of catalysis by the competing enzyme systems. Knowing the values of $v_{max(R)}/v_{max(S)}$, $v_{max(R)}/K_R$, and $v_{max(S)}/K_S$, one can calculate *ee* as $A_0 \to 0$ [eq. (m)] and as $A_0 \to \infty$ (saturation) [eq. (n)].

$$ee = \frac{\dfrac{v_{max(R)}}{K_R} - \dfrac{v_{max(S)}}{K_S}}{\dfrac{v_{max(R)}}{K_R} + \dfrac{v_{max(S)}}{K_S}} \qquad (m)$$

$$ee = \frac{v_{max(R)} - v_{max(S)}}{v_{max(R)} + v_{max(S)}} \qquad (n)$$

These values provide a useful overview of the upper and lower limits of optical purity that are theoretically obtainable for each substrate. Moreover, structural changes in substrates can be quantitatively correlated to changes in z and y, which serve as measures of the relative changes in binding and catalysis of competing enzyme systems. Optimization of enantioselectivity is dependent on the maximization of z.

3. Enantioselective Reductions

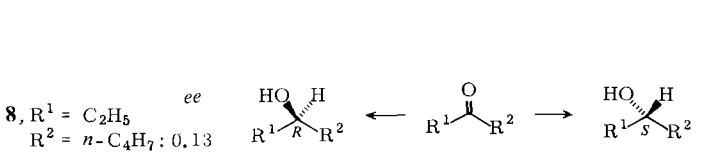
Much of the early work on the microbial reduction of ketones and keto acids or keto esters has been amply de-

scribed and reviewed[14]. Hence, we shall confine our treatment here to more recent studies on enantioselective reductions of prochiral ketones, highlighting the relationship of substrate structure to enantioselectivity; diastereoselective reductions will not be discussed.

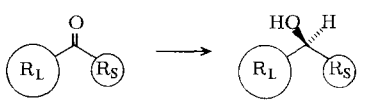
3.1. Alkanones

The purified NADPH-specific dihydroxyacetone reductase of *Mucor javanicus*[15], an enzyme that transfers hydrogen exclusively to the *Si*-face of the carbonyl group of most substrates, has been extensively investigated by the Prelog school. The unique structure of the active site of this enzyme allows it not only to possess broad substrate-specificity but also high enantioselectivity. Although the value of k_{cat}/K decreases markedly on changing the substrate from dihydroxyacetone to 2-alkanones such as acetone, the reaction rate is enhanced significantly when the alkyl chain is increased in length. Product analysis demonstrated that with the exception of 2-butanone, where the racemic alcohol was obtained, the higher homologues were reduced with high enantioselectivity ($ee = 0.94$) to the (*R*)-alcohols—(*R*)-2-pentanol, (*R*)-2-hexanol, and (*R*)-2-octanol. From this, it was concluded that the ethyl group of 2-butanone is too short to create the necessary hydrophobic interactions. Hence, 2-butanone is attacked by hydrogen at both the *Si* and *Re*-face to yield racemic 2-butanol.

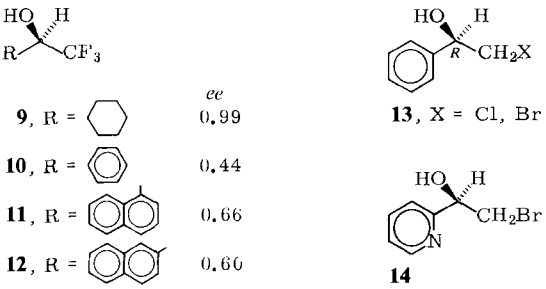
The first systematic study of the stereochemical course of reduction of acyclic ketones by bakers' yeast *(Saccharomyces cerevisiae)* was reported by *MacLeod* et al.[16]. They examined the reduction of a series of ketones with all combinations of the substituents methyl, ethyl, *n*-propyl, *n*-butyl, and phenyl. With the exception of the alcohol derived from butyl ethyl ketone **8**, where the *R*-configuration is preferred, the secondary alcohols **1**—**7** possess the *S*-configuration in excess. The more sterically hindered ketones, including *n*-butyl *n*-propyl ketone, *t*-butyl methyl ketone, isobutyl isopropyl ketone, and *n*-amyl phenyl ketone, were not reduced by yeast. Similar results were obtained by other groups[1b, 17].



These results suggested that the stereochemical course of reduction proceeds in contrast to that with dihydroxyacetone reductase from *Mucor javanicus*, via hydrogen transfer to the *Re*-face of the prochiral ketone, R_S and R_L represent the smaller and larger group, respectively.



This is now known as the Prelog rule[18], and was initially postulated for the reduction of decalones by *Curvularia lunata*. Subsequently, however, this rule has been widely used to predict the stereochemistry of alcohols produced in microbial reductions. In accord with this rule, the *R*-configurated trifluoromethyl alcohols[19] **9**—**12** are obtained in excess by reduction of the corresponding ketones with baker's yeast. A similar stereochemical trend is observed in other microbial reductions of aryl α-halomethyl ketones, which yield (*R*)-halohydrins **13** ($ee \geq 0.80$)[20]. It thus appears that monosubstituted methyl groups are effectively smaller than a phenyl ring. Apparently, the presence of a heteroatom in the aromatic system, as in **14**, does not influence the stereochemical course of the reduction.



Two alternative explanations have been proposed to account for the partial enantioselective reductions of ketones by fermenting yeast[16]. The yeast alcohol dehydrogenase (YADH) reduces ketones, but is partially enantioselective with unnatural ketones. Alternatively, more than one oxidoreductase exists (including YADH and/or a yet unknown oxidoreductase) which produces alcohols of opposite configuration at different rates. *MacLeod* et al.[16] favor the first of these two explanations, but it is not possible at present to draw definite conclusions. Although crystalline YADH has been shown to reduce most of the aforementioned acyclic ketones at different rates[27], until the alcohols obtained from each of these substrates have been isolated, purified, and the optical purities defined, generalizations cannot be made about this complex system, especially since other enzymes in yeast may also competitively reduce these ketones.

	ee
1, $R^1 = CH_3$, $R^2 = C_2H_5$:	0.67
2, $R^1 = CH_3$, $R^2 = n\text{-}C_3H_7$:	0.64
3, $R^1 = CH_3$, $R^2 = i\text{-}C_3H_7$:	0.90
4, $R^1 = CH_3$, $R^2 = n\text{-}C_4H_9$:	0.82
5, $R^1 = CH_3$, $R^2 = -(CH_2)_3C{\equiv}CH$:	0.99
6, $R^1 = C_2H_5$, $R^2 = n\text{-}C_3H_7$:	0.12
7, $R^1 = CH_3$, $R^2 = C_6H_5$:	0.89

3.2. β-Keto Esters and Acids

The asymmetric reduction of ethyl acetoacetate by bakers' yeast is a well-established method for the synthesis of (*S*)-ethyl 3-hydroxybutanoate **15**, a valuable chiral building block. However, the yield (60—80%) and the optical purity ($ee = 0.85$—0.97) of the product vary depending on the procedure used[21]. The most critical factor affecting the enantioselectivity of this reduction is the substrate concentration, because of the presence of competing enzymes

of opposite chirality in bakers' yeast. The optical purity of the product drops significantly when the concentration of ethyl acetoacetate is greater than 5 g/L[22]. Because the (*S*)-enzyme(s) has (have) a competitive advantage by virtue of having a higher v_{max}/K ratio than that of the *R*-enzyme(s), optically pure (*S*)-ethyl 3-hydroxybutanoate can be obtained by limiting the concentration of ethyl acetoacetate in the reaction medium via continuous, slow addition of the substrate[22]. If the apparent values of y, K_R and x are determined, one may calculate the *ee* for any substrate concentration[13] [eq. (l)]; in turn, this allows the definition of the optimum rate of continuous substrate addition.

Whereas ethyl acetoacetate[21] and acetoacetic acid[23] are reduced mainly to their corresponding (*S*)- (or L)-isomers, ethyl 3-oxopentanoate[24], 3-oxohexanoic acid[23], 3-oxoheptanoic acid[23], and 3-oxo-6-heptenoic acid[1a] are all preferentially converted into their respective (*R*)-(or D)-isomers **16**—**19**. These results suggest that by extending the length of the hydrocarbon chains of the β-keto carbonyl molecule the stereochemical course of yeast reduction may be altered from L to D. The reduction of ethyl 4-chloroacetoacetate to (*S*)-ethyl 4-chloro-3-hydroxybutyrate **20**[25] and of ethyl benzoylacetate to (*S*)-ethyl 3-hydroxy-3-phenylpropionate **21**[26] are also consistent with this supposition. The *S*-configuration of **20** and **21** is a consequence of the sequence rule.

The enantioselectivity of the reduction of β-keto carbonyl compounds by yeast is also strongly influenced by

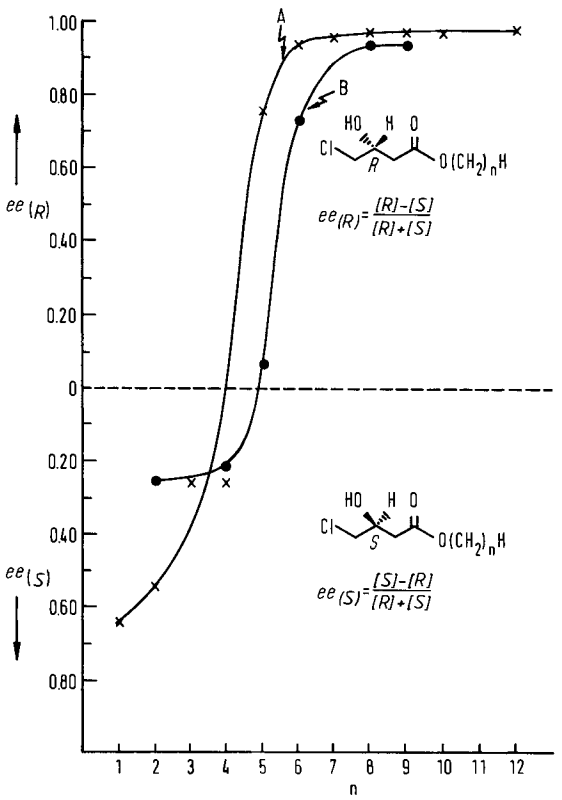
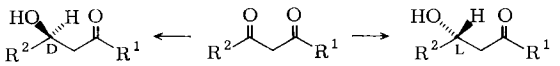


Fig. 2. Enantiomeric excess (*ee*) as a function of the size of the ester group of 4-chloro-3-oxobutanoate. Curve A: 0.045 M; curve B: 0135 M. See also text.

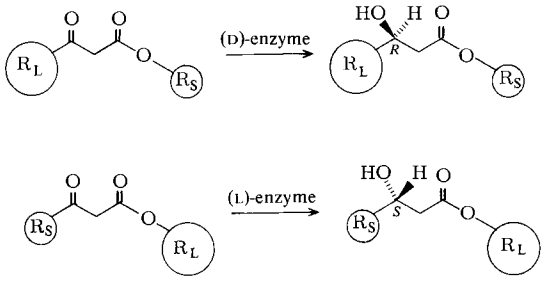
	ee
16, R^1 = OC_2H_5, R^2 = CH_2CH_3 :	0.40
17, R^1 = OH, R^2 = $CH_2CH_2CH_3$:	≈1.0
18, R^1 = OH, R^2 = $CH_2CH_2CH_2CH_3$:	≈1.0
19, R^1 = OH, R^2 = $CH_2CH_2CH{=}CH_2$:	0.99
20, R^1 = OC_2H_5, R^2 = CH_2Cl :	0.55
21, R^1 = OC_2H_5, R^2 = C_6H_5 :	≈1.0



	ee
15, R^1 = OH, OC_2H_5, R^2 = CH_3 :	0.95
22, R^1 = OC_8H_{17}, R^2 = CH_2CH_3 :	0.99
23, R^1 = OC_8H_{17}, R^2 = $CH_2CH_2CH_3$:	0.71
24, R^1 = $-\overset{H}{N}-Ph$, R^2 = CH_2Cl :	0.97

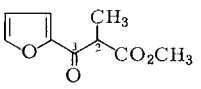
changes in the carboxy substituents (R^1). Along a homologous series of C_1- to C_{12}-esters of 4-chloroacetoacetic acid as substrates, a dramatic shift in the stereochemistry of the alcohol products was observed as the size of the ester group was enlarged (Fig. 2). Curve A depicts that the methyl ester was reduced to its corresponding (*S*)-enantiomer ($ee_{(S)}=0.65$), whereas the octyl ester was reduced to its (*R*)-enantiomer ($ee_{(R)}=0.97$). Notably, the $ee_{(R)}$-value of the pentyl ester dropped from 0.76 to 0.07 when the concentration of the substrate was raised from 0.045 M to 0.135 M (curve B)[25]. Similarly, octyl 3-oxopentanoate and octyl 3-oxohexanoate were reduced in excess to their corresponding (*S*)-isomers **22** and **23**, respectively[27].

Substrates with aromatic substituents at the carboxy end (R^1) are also transformed by bakers' yeast predominantly into (*R*)-configurated alcohols. *N*-Phenyl 4-chloro-3-oxobutanamide (3 mg/mL) was reduced to (*R*)-*N*-phenyl 4-chloro-3-hydroxybutanamide **24** ($ee_{(R)}=0.97$), but at 8 mg/mL the optical purity of the alcohol dropped drastically ($ee_{(R)}=0.04$)[27]. Hence, the stereochemical course of the reduction of β-keto carboxylic acid derivatives by yeast is influenced by substituents at both ends of the molecule. While the enantioselective reductions are dependent on the ratio of the apparent v_{max}/K-values of the two types of competing enzymes of opposite chirality, the enzyme(s) affording (*S*)- (or L)-alcohols appear to prefer large hydrophobic substituents at the carboxy end, whereas the (D)-enzyme(s) appear to prefer those at the hydrocarbon end (R^2). Recent results also support this contention[28].



There are many oxidoreductases in bakers' yeast that could be responsible for catalyzing the reduction of these β-keto carboxylic acid derivatives. However, crystalline YADH I (EC 1.1.1.1) and purified yeast L-LDH (EC 1.1.1.27) do not reduce ethyl or octyl 4-chloroacetoacetate[27]. On the other hand, β-hydroxyacyl CoA dehydrogenase from porcine heart[29] (EC 1.1.1.35), an enzyme involved in the degradation of fatty acids, reduced both keto esters in the presence of NADH to their respective (*R*)-4-chloro-3-hydroxybutyrates (*ee* = 0.98)[27]. Furthermore, we have recently found that purified fatty acid synthetase from bakers' yeast[30] readily reduces both ethyl and octyl 4-chloroacetoacetates in the presence of NADPH to their respective (*S*)-4-chloro-3-hydroxybutyrates (*ee* = 0.98)[31]. The purification of the β-hydroxyacyl CoA dehydrogenase from bakers' yeast is currently in progress. These two enzymes are probably the major ones responsible for the reduction of these unnatural β-keto carboxylic acid esters, since the normal physiological substrates of β-hydroxyacyl CoA dehydrogenase (a mitochondrial enzyme) and the β-keto reductase component of fatty acid synthetase are the structurally analogous acetoacetic thiol esters. Furthermore, the first enzyme generates alcohols having an (L)-configuration, whereas the second generates alcohols having a (D)-configuration. It is interesting to note that mammalian fatty acid synthetase[32] appears to possess a very relaxed substrate specificity, because the keto reductase component of this complex also reduces cyclic ketones.

Reduction of ethyl acetoacetate with *Geotrichum candidum* leads to (*R*)-ethyl 3-hydroxybutyrate of moderate optical purity (*ee* = 0.89) in an overall yield of 36%[22]. However, this reaction is highly dependent on the metabolic state of cells, and the optical yield was poorly reproducible, again suggesting the presence of competing enzymes with the (*R*)-type dominating in this case. On the small scale, it is probably more convenient to prepare (*R*)-ethyl 3-hydroxybutyrate by using either the dihydroxyacetone reductase of *Mucor javanicus* or the commercially available D-β-hydroxybutyrate dehydrogenase (EC 1.1.1.30) of *Pseudomonas lemoignei*[27]. Both enzymes catalyze the reduction of ethyl acetoacetate with high enantioselectivity (*ee* > 0.97), but an NADH-regenerating system[33] must be included in the incubation.



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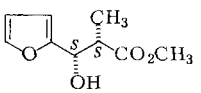
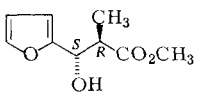
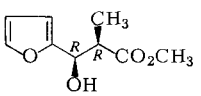
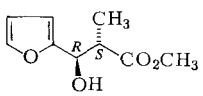


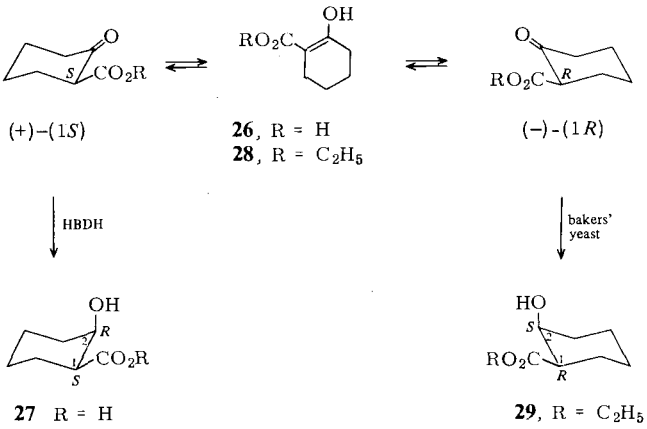






Because the α-methyl-β-hydroxy structural element appears in a variety of natural products, α-methyl-β-keto esters are attractive substrates for asymmetric reduction. The action of a wide variety of microorganisms on methyl 3-(2-furyl)-2-methyl-3-oxopropionate **25** has been studied[34]. All four possible stereoisomers were prepared by selecting the appropriate microorganism. With most microorganisms, a mixture of the (2*R*,3*R*)-ester (*ee* = 0.49—0.90) and the (2*S*,3*R*)-ester (*ee* = 0.23—0.91) was obtained in a ratio of ca. 1:1 to 4:6. The exception was *Candida albicans* KSY-36 which gave only the (2*S*,3*R*)-ester (*ee* = 0.99), but in 23% yield. In contrast, *Kloeckera saturnus* KSY-7 afforded a ca. 1:1 mixture of the (2*S*,3*S*)-ester (*ee* = 0.68) and the (2*R*,3*S*)-ester (*ee* = 0.46) in 29% yield. Ethyl α-methylacetoacetate was reduced by bakers' yeast to afford a 9:91 mixture of the (2*R*,3*S*)- and (2*S*,3*S*)-esters in 65% yield, whereas ethyl α-allylacetoacetate was reduced to a 96:4 mixture of the (2*R*,3*S*)- and (2*S*,3*S*)-esters in 84% yield[35]. Bakers' yeast also reduces several ethyl α-formylpropionates to yield predominantly the (−)-(*R*)-ester (*ee* = 0.60—0.65), which may be crystallized via the 3,5-dinitrobenzoate to give the enantiomerically pure ester[36].

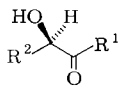
Since 2-oxocyclohexanecarboxylates are conformationally constrained analogues of acetoacetate, it was anticipated that compounds of this type might also serve as substrates for those enzyme systems that reduce acetoacetate. With purified D-3-hydroxybutyrate dehydrogenase (HBDH) from *Rhodopseudomonas spheroides* in the presence of NADH, it was shown that 2-oxocyclohexanecarboxylic acid **26** was reduced exclusively to *cis*-(1*S*,2*R*)-2-hydroxycyclohexanecarboxylic acid **27** in 77% yield, indicating that the (+)-(1*S*)-enantiomer was selectively reduced by HBDH[37]. On the other hand, bakers' yeast,

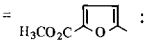


which reduces ethyl acetoacetate to (*S*)-ethyl 3-hydroxybutyrate, would be expected to selectively attack the (−)-(1*R*)-enantiomer. In fact, ethyl 2-oxocyclohexanecarboxylate **28** was indeed reduced to the (1*R*,2*S*)-isomer **29** in 69% yield and 2-oxocyclopentanecarboxylic acid was similarly transformed into its corresponding (1*R*,2*S*)-isomer in 80% yield[26]. Similar results were obtained with the corresponding tetrahydrothiophene analogues[38]. The alternative possibility involving the stereospecific reduction of the enol, which is known to be the major species in the equilibrium mixture, is unlikely in light of results on the reduction of related compounds[39].

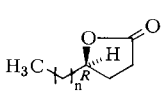
3.3. Other Keto Esters and Acids

Derivatives of 2-aryl-2-oxoacetic acid are generally reduced by bakers' yeast to give satisfactory yields of optically pure α-hydroxy acids **(30–33)**[26]. Thus, methyl 2-oxo-2-phenylacetate gave (−)-(*R*)-methyl 2-hydroxy-2-phenylacetate **30** in 59% yield; 2-oxo-2-phenylacetamide gave (−)-(*R*)-2-hydroxy-2-phenylacetamide **31** in 70% yield; and ethyl-2-thienylacetate gave (−)-(*S*)-ethyl 2-thienylacetate **33** in 49% yield. In contrast, reduction of methyl 2-oxo-3-phenylpropionate yielded only racemic methyl 2-hydroxy-3-phenylpropionate **34**. Also, 2-oxoalkanoic acid esters did not produce optically pure alcohols. Ethyl pyruvate was reduced to (+)-L-ethyl lactate (*ee* = 0.92), but this was racemized in the reaction medium, suggesting the presence of a racemase. The enzymology of the reduction of these α-keto acid derivatives has not been investigated, but bakers' yeast is known to contain L- and D-lactate dehydrogenases that are known to react with α-hydroxy acids. Furthermore, purified YADH in the presence of NADH reduced pyruvate to (−)-D-lactate[40]. An NADH-dependent 2-oxocarboxylate reductase has been found in several anaerobic bacteria, and this enzyme produces (2*R*)-hydroxy acids[41].

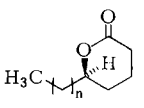


		ee
30, R^1 = OCH_3, R^2 = C_6H_5	:	≈1.0
31, R^1 = NH_2, R^2 = C_6H_5	:	≈1.0
32, R^1 = OCH_3, R^2 = 	:	0.92
33, R^1 = OC_2H_5, R^2 =	:	high
34, R^1 = OCH_3, R^2 = $C_6H_5CH_2$	:	0.0

Optically-active hydroxy acids (isolated as (+)-lactones) may be readily prepared by yeast reduction of γ- and δ-keto acids. With the bacterium *Sarcina lutea* and the mold *Cladosporium butyri*, the corresponding (−)-lactone was obtained by reduction of δ-ketohexanoic acid[42]. The (*S*)-configuration was assigned to (−)-γ-valerolactone since the (+)-γ-lactones should have the (*R*)-configuration[43].



n = 4-7

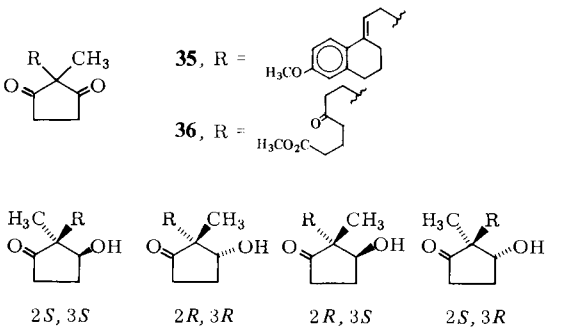


n = 2-5

The enzyme in yeast responsible for the reduction of 5-oxodecanoid acid occurs in the mitochondrial fraction, is NADPH-dependent, and the reaction is strongly stimulated by the addition of ATP and Mg^{2+}, but to a lesser extent by coenzyme A[44]. It is not yet known whether this enzyme is 3-hydroxyacyl CoA dehydrogenase, although the latter is NADH-dependent.

3.4. Cyclic Diketones

The asymmetric reduction of cyclopentane-1,3-diones with 2,2-dialkyl substituents has been examined in considerable detail[45], because this reaction has found application in the industrial total synthesis of steroid hormones. The stereochemical course of this reduction depends on the relative size of the 2,2-dialkyl substituents and on the microorganisms, and can be carried out with a high degree of enantioselectivity. For example, *Saccharomyces uvarum*



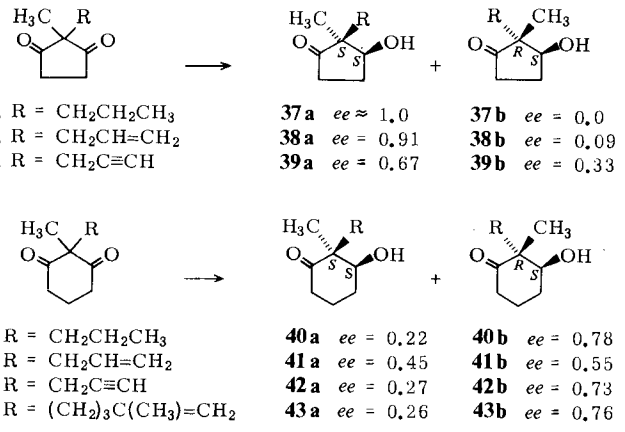
(CBS 1508) reduces **35** to give the (2*R*,3*S*)-isomer in 74% yield, accompanied by a small quantity of the (2*S*,3*S*)-isomer as by-product. In contrast, the bacterium *Bacillus thuringiensis* transformed **35** into predominantly the (2*S*,3*S*)-isomer in 87% yield. With most microorganisms, alcohols of the 3*S*-configuration are produced, although some strains of *Kloeckera* afforded alcohols of the *R*-configuration[45].

Similarly, yeasts of the genera *Schizosaccharomyces* and *Saccharomyces* convert **36** into the (2*R*,3*S*)-isomer as the major product, with the (2*S*,3*S*)-isomer as the only by-product. It is notable that a variety of α,β-unsaturated ketones, e.g. acrolein, methyl vinyl ketone, ethynyl methyl ketone, 2-cyclohexen-1-one, and also allyl alcohol, are capable of enhancing the rate and extent of formation of the (2*R*,3*S*)-isomer and reduce the level of (2*S*,3*S*)-isomer formation[46]. Although the mechanism of action of these "enhancers" is not known, one possibility could be that they act as "suicide substrates" for the oxidoreductase which forms the undesired (2*S*,3*S*)-isomer, for allyl alcohol has been reported to be a suicide substrate for YADH[47].

In a more recent study, *Brooks* et al.[48] conducted investigations designed to establish a relationship between enantioselectivity and size differences of both alkyl substituents in the 2-position. As expected, whereas (*S*)-alcohols were produced in both series, the enantioselectivity of the reaction was found to be strongly dependent not only on the alkyl substituents but also on the ring size. In the cyclopentane series, the (2*S*,3*S*)-isomers **37a**—**39a** were the major species, whereas the (2*R*,3*S*)-isomers **40b**—**43b** predominated in the cyclohexane series.

4. Outlook

Microbial, enantioselective reduction of ketones is now recognized as a method of great value for the preparation



37, R = $CH_2CH_2CH_3$	**37a** *ee* ≈ 1.0	**37b** *ee* = 0.0
38, R = $CH_2CH{=}CH_2$	**38a** *ee* = 0.91	**38b** *ee* = 0.09
39, R = $CH_2C{\equiv}CH$	**39a** *ee* = 0.67	**39b** *ee* = 0.33

40, R = $CH_2CH_2CH_3$	**40a** *ee* = 0.22	**40b** *ee* = 0.78
41, R = $CH_2CH{=}CH_2$	**41a** *ee* = 0.45	**41b** *ee* = 0.55
42, R = $CH_2C{\equiv}CH$	**42a** *ee* = 0.27	**42b** *ee* = 0.73
43, R = $(CH_2)_3C(CH_3){=}CH_2$	**43a** *ee* = 0.26	**43b** *ee* = 0.76

of chiral alcohols. Since the stereochemical course of reduction is dependent on the nature of the substituents attached to the carbonyl group, the Prelog rule has been applied with some degree of success to predict the stereochemical outcome for microbial reductions. However, in intact cell systems the ketone substrate may be acted upon by competing oxidoreductases of opposite chirality, and the rates of production of unequal quantities of enantiomeric alcohols are dependent on the kinetic parameters (K and v_{max}) of the respective competing enzymes. Hence, it is often feasible to regulate the stereochemical course of reduction by designing suitable substrates with significant differences in v_{max} and/or K values for the competing enzyme systems.

It is to be expected that major efforts in the near future will focus on the isolation and characterization of the relevant oxidoreductases, and that a correlation of substrate structure with the kinetic parameters v_{max} and K of these enzymes will be made. This information should not only provide a conceptual framework for better interpretation of the complexity of microbial reductions of ketonic substrates, but also aid in the development of strategies to control enantioselectivity. Selective inhibitors such as "suicide substrates" may then be designed to inhibit the dominant interfering enzyme. Furthermore, various mutants may be selected, and hence chiral alcohols of either configuration and high optical purity may be made accessible in larger quantities.

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Mercury(II)- and Palladium(II)-Catalyzed [3,3]-Sigmatropic Rearrangements

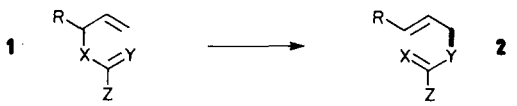
New Synthetic Methods (46)

By Larry E. Overman*

Mercury(II) and palladium(II) salts have found broad applications as catalysts for [3,3]-sigmatropic rearrangements leading to formation of C–O, C–N, C–S, and C–C σ bonds. Increases in reaction rate are often very large (10^{10}–10^{14} at 1 M catalyst concentration) and allow many previously difficult transformations to be conducted at or near room temperature, often with attendant increases in stereoselectivity and decreases in by-product formation. The mechanism of these catalyzed transformations is briefly discussed, and evidence is summarized to suggest that many follow a cyclization-induced rearrangement mechanism.

1. Introduction

[3,3]-Sigmatropic rearrangements[1,2] (Scheme 1) are among the more important transformations in the arsenal of modern synthetic organic chemistry[3]. These reactions allow the allylic interchange of functionality X and Y (**1**→**2**), and often fashion the newly formed CC double bond with high levels of stereocontrol[3c,4].



Scheme 1. The newly formed C-Y bond is sketched with a bold line.

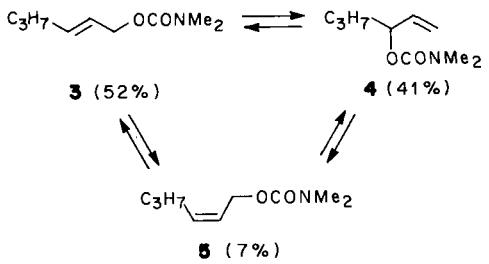
It is not surprising that the development of catalytic methods[5] for these important transformations has attracted widespread attention, and this area has recently been reviewed comprehensively by *Lutz*[6]. Acid-base catalysis has been most extensively investigated and requires the presence of an acidic or basic heteroatom substituent. The most important transformations of this type are Brønsted and Lewis acid catalyses of aromatic Claisen, aromatic amino-Claisen and Cope rearrangements, as well as base-catalysis of the oxy-Cope rearrangement and the Claisen rearrangement of allylic esters[6]. Catalysis of [3,3]-sigmatropic rearrangements by a variety of metals and organometallic reagents has also been described[6]. A representative, though certainly not complete, list of metal "catalysts"[5] includes Ni^0, Pd^0, Ag^I, Ni^{II}, Pd^{II}, Pt^{II}, Hg^{II}, and Al^{III} compounds.

Perhaps the most versatile of the metal catalysts are the "soft"[7] metal salts of Hg^{II} and Pd^{II}. These effectively catalyze a wide variety of [3,3]-sigmatropic rearrangements which form C–O, C–N, C–S, and C–C bonds (C–Y, Scheme 1). Catalyzed transformations of this type occur under extremely mild conditions (neutral pH and at, or near, room temperature) and often afford yields and regio- and stereoselectivities which far exceed those of their thermal counterparts.

This review briefly summarizes recent advances in the catalysis of [3,3]-sigmatropic rearrangements with Hg^{II} and Pd^{II} salts. Excluded are the many useful [3,3]-sigmatropic rearrangements effected with Pd^0 complexes[6,8,9].

2. Allylic Ester Rearrangements

Catalysis of the equilibration of allylic esters by mercury(II) salts was first reported by *Overman* and *Campbell* in 1976[10,11]. Allylic carbamates equilibrated more readily than allylic anisoates or acetates[10,12], and *anhydrous* mercury(II) trifluoroacetate[11] was found to be the catalyst of choice. For example, treatment of the hexenyl carbamates **3** and **4** with mercury(II) trifluoroacetate in the molar ratio 1:0.4 gave the equilibrium mixture of **3**, **4**, and **5** within 4 h at room temperature (Scheme 2). However, the (*Z*)-



Scheme 2.

isomer **5** reacted much more slowly and could not be fully equilibrated with **3** and **4**[11,13]. Comparison of the initial rate of the mercury(II) trifluoroacetate-catalyzed isomerization of **3** in tetrahydrofuran (THF) with the thermal, gas-phase isomerization of several 2-butenyl esters[13] indicated a rate enhancement of 10^{12}–10^{13} (1 M catalyst concentration) for the mercury(II)-catalyzed transformation.

A number of other mercury(II) trifluoroacetate-catalyzed allylic ester rearrangements are summarized in Scheme 3. The only limitation reported to date is the unreactivity of 2-alkylallylic esters, e.g. **6**[11,14]. This method for equilibrating allylic alcohol derivatives, which typically affords high yields, has significant advantages over classical acid-catalyzed procedures which proceed via allyl cation intermediates[15]. Thus, *N,N*-dimethyllinalyl carbamate

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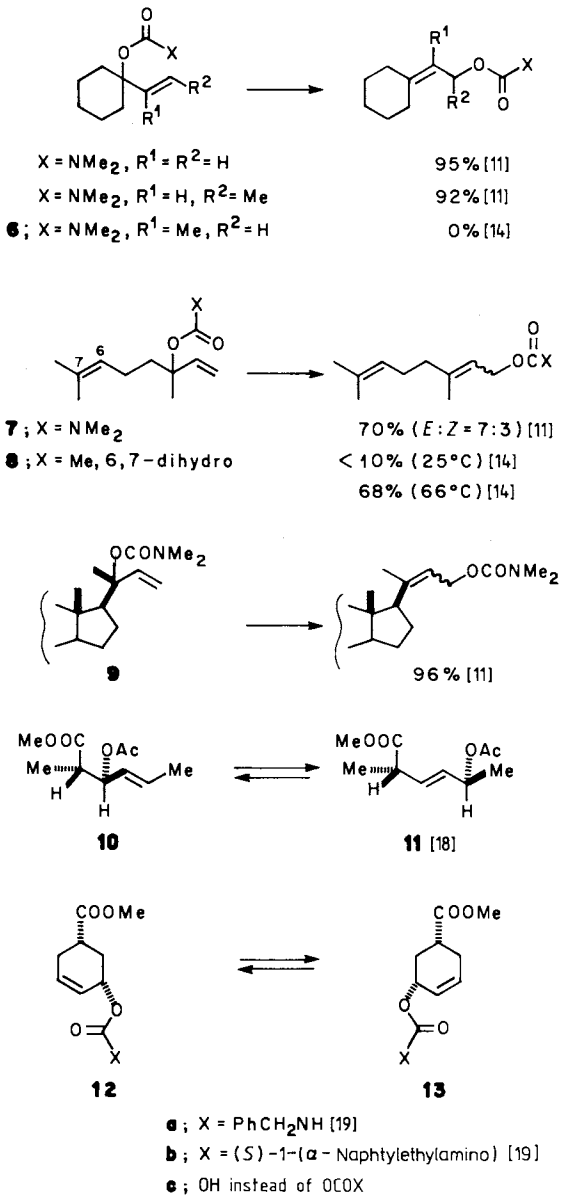
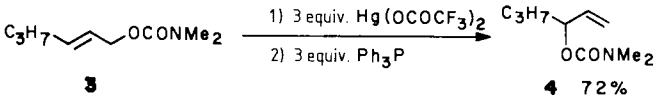


Scheme 3. Representative examples of mercury(II) trifluoroacetate-catalyzed allylic ester rearrangements [a] (in THF at 25—66°C; molar ratio allylic ester : $Hg(OCOCF_3)_2$ = 1 : 0.25—0.4).

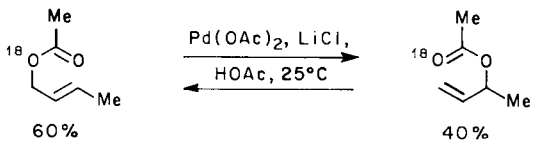
7 was converted[11] into the geranyl and neryl isomers without competing cyclization[16], and the allylic rearrangement[11] of the steroidal ester **9** was accomplished in nearly quantitative yield without complicating dehydration or skeletal rearrangement[17]. Of equal significance is the clean suprafacial chirality-transfer of mercury(II)-catalyzed allylic ester rearrangements[18,19]. This feature was demonstrated by *Eschenmoser* et al.[18] in the stereospecific interconversion of acetates **10** and **11**, and by *Trost* et al.[19] in the mercury(II)-catalyzed racemization of the optically pure cyclohexenyl carbamate **12a**. Mercury(II) trifluoroacetate-catalyzed equilibration of the mixture of diastereomeric carbamates formed from *rac*-methyl *cis*-5-hydroxy-3-cyclohexenecarboxylate and (*S*)-1-(α-naphthyl)ethylisocyanate yielded **13b** and **12b** in the ratio 2 : 1. Chromatographic separation of **13b** followed by re-equilibration of the unwanted diastereomer **12b** provided a new method for converting a symmetrical allylic alcohol racemate into a single enantiomeric product[19]. Enantiomerically pure alcohol **13c** obtained in this way was used by *Trost* et al.[19] to prepare optically pure prostanoid analogues.

Use of an excess of mercury(II) trifluoroacetate followed by treatment of the reaction mixture with triphenylphosphane provides a method of achieving "contra"-thermodynamic allylic isomerizations (see Scheme 4)[11,12]. However, this approach is limited in scope and works well only when the two isomers have similar energies[11,20].



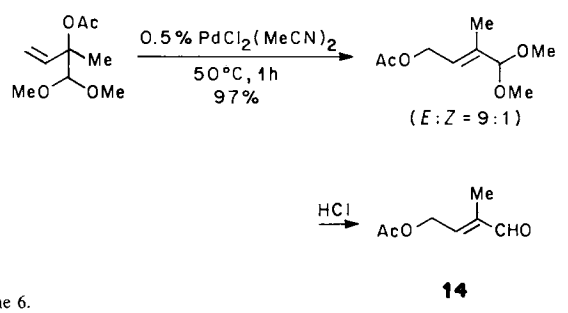
Scheme 4.

Palladium(II) salts are even more effective than mercury(II) salts for equilibrating allylic esters[21]. Catalysis by palladium(II) was first recognized by *Winstein* et al.[22] in their investigations of the oxidation of alkenes with palladium acetate in acetic acid. Subsequently, this reaction was studied extensively by *Henry*[23,24], who convincingly demonstrated the involvement of two equilibration processes which proceed with and without exchange of the ester acyl group with acetic acid. The intramolecular equilibration reaction was found to occur 500 times faster with propionate than with trifluoroacetate esters, and with complete 1,3-shift of the oxygen atoms (Scheme 5)[24b]. Allylic esters are also equilibrated at higher temperatures (70—100°C) by palladium acetate or palladium acetylacetonate in the presence of phosphane ligands[25].



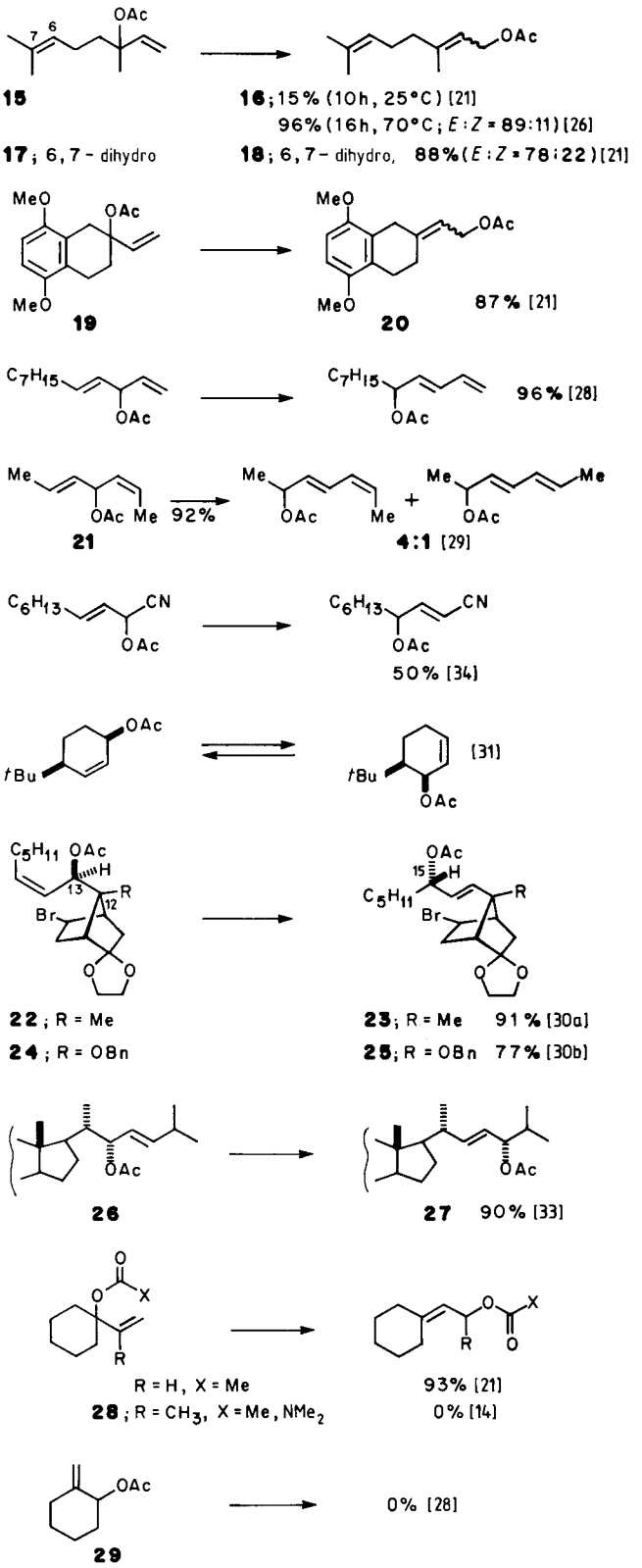
Scheme 5.

For preparative purposes the most convenient method for equilibrating allylic esters is to use the palladium(II) chloride complexes of acetonitrile or benzonitrile in inert solvents such as THF, benzene, dichloromethane, or dichloroethylene. This procedure was first described by *Meyer*[26], and his synthesis of the terpene intermediate **14** is shown in Scheme 6. This method was further developed by *Overman* and *Knoll*[21], who showed that a variety of al-



Scheme 6.

lylic acetates could be conveniently equilibrated at room temperature in the presence of 4 mol-% of $PdCl_2(MeCN)_2$. Measurements of the initial rate[27] of the palladium(II) chloride-catalyzed rearrangement of (*E*)-2-hexenyl acetate at 25°C in THF showed that this conversion was ca. ten times faster than the rearrangement of hexenyl carbamate



Scheme 7. Representative examples of palladium(II) chloride-catalyzed allylic ester rearrangements [a] (at 25°C; molar ratio allylic ester : $PdCl_2(RCN)_2 = 1 : 0.01-0.08$).

3 under similar conditions, but catalyzed by mercury(II) trifluoroacetate. This experiment allowed a rate enhancement of $10^{13}-10^{14}$ (1 M catalyst concentration) to be estimated[11,14] for $PdCl_2$-catalysis.

A representative selection of allylic ester equilibrations catalyzed by palladium(II) chloride is summarized in Scheme 7. These results reveal that carbamates rearrange more rapidly than acetates[14,28], which in turn react somewhat faster than carbonates[28]. In contrast to the facile rearrangement of **17** with $PdCl_2$ (4 mol-%, 2 h, 25°C), this ester was unchanged after one week at room temperature in the presence of 20 mol-% of tetrakis(triphenylphosphane)palladium(0)[14]. Like the corresponding mercury(II)-catalyzed equilibrations, allylic ester rearrangements catalyzed by palladium(II) chloride are not complicated by skeletal rearrangements, cyclizations (cf. clean conversion of **15** into **16**), or elimination processes (e.g. clean conversion of **19** into **20**) which often plague[11,16,17] acid-catalyzed equilibrations[15]. There are many other similarities between the Hg^{II}- and Pd^{II}-catalyzed reactions. Thus, (*Z*)-alkenes rearrange much slower[14,28,29] than the corresponding (*E*)-isomers (note selective rearrangement of **21**) in the presence of palladium(II) chloride, and with clean suprafacial stereochemistry[30-33]. This latter feature has been exploited by *Grieco* et al.[30] to obtain the desired stereochemistry at the C-15 center of prostanoids. A key step in this prostaglandin synthesis was the palladium(II) chloride-catalyzed rearrangement of **22** and **24** to give the rearranged (*E*)-allylic acetates **23** and **25**, respectively, which were subsequently converted into 12-methyl-$PGF_{2\alpha}$ and 12-hydroxy-$PGF_{2\alpha}$[30]. Importantly, the rearrangement of the C-13 epimer of **22** (not shown in Scheme 7) was also demonstrated to be suprafacial and cleanly yielded the C-15 epimer of **23**[30]. The apparent irreversibility of these rearrangements was suggested[30] to be a consequence of destabilizing steric interactions of the acetate group with the *exo*-bromine and the quaternary C-12 center. *Ikekawa* et al.[33] have reported a similar, apparently irreversible transfer of chirality from C-22 to C-24 (e.g. **26** → **27**) in steroidal side chains.

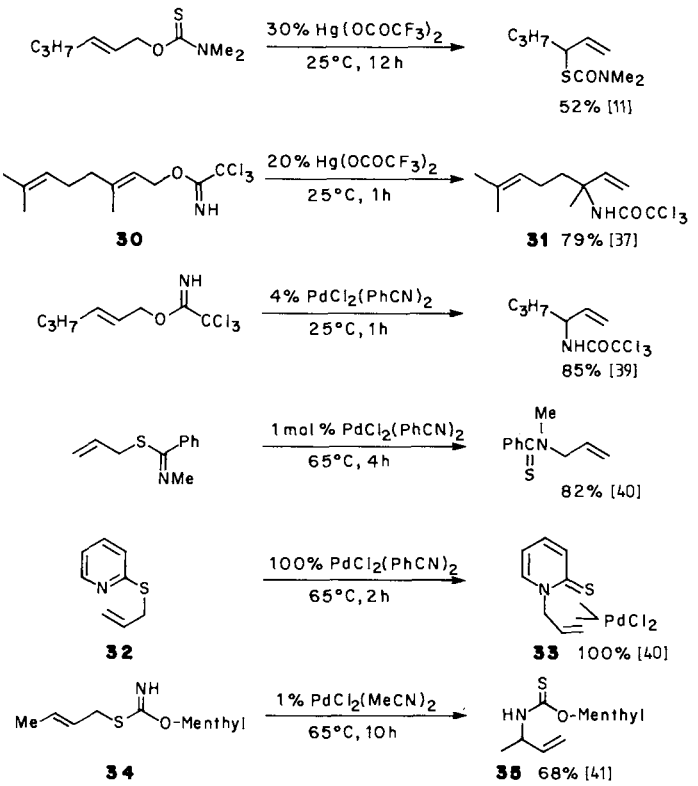
Like the mercury(II)-catalyzed reaction, allylic ester rearrangements catalyzed by palladium(II) chloride are limited to allylic esters which are unsubstituted at the C-2 position of the allyl group (e.g. **28** and **29** do not react). Another limitation would appear to be the failure of propargylic allylic acetates (1-ethynylallyl acetates) to rearrange in the presence of palladium(II) chloride[28,35,26].

In summary, it would appear that for most applications palladium(II) chloride should be the catalyst of choice, since allylic rearrangements are faster than with mercury(II) salts and can be accomplished using less catalyst. A possible exception would be substrates which contain ligands that coordinate strongly to palladium(II), such as dienes[21] and alkynes[28,35].

3. Other Hetero-Cope Rearrangements

A variety of other hetero-Cope rearrangements are catalyzed by mercury(II) and palladium(II) salts, and representative examples are summarized in Scheme 8. Catalysis of

[3,3]-sigmatropic rearrangements by mercury(II) compounds was first discovered in our laboratory ten years ago during studies of the allylic imidate→allylic amide conversion (e.g. **30**→**31**)[37,3e]. This transformation can also be brought about by salts of platinum(II)[38] and palladium(II)[3e,39]. *Yoshida* et al.[40] have reported several examples of the conversion of *S*-allylthioimidates into *N*-allylthioamides catalyzed by palladium(II) chloride. In this case, palladium(II)-catalysis is particularly important since the corresponding thermal reactions often afford entirely different products[40]. Particularly noteworthy is the conversion of **32** into the palladium(II) chloride complex **33**, which demonstrates the use of palladium complexation to shift an unfavorable equilibrium [1-allyl-2-thiopyridone (non-complexed **33**) is less stable than **32**][40]. This would



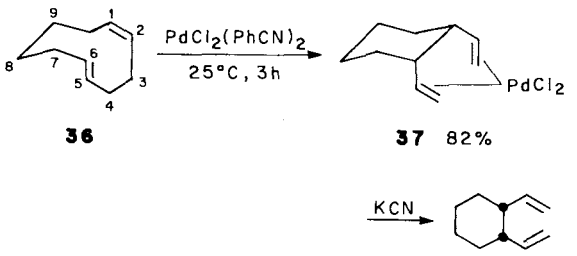
Scheme 8. Representative examples of mercury(II)- and palladium(II)-catalyzed hetero-Cope rearrangements.

appear to be a strategy which is potentially more generally applicable. The $PdCl_2$-catalyzed rearrangement of *S*-allyl-(*O*-(−)-methyl) iminothiocarbonates (e.g. **34**→**35**) to *N*-allyl *O*-((−)-menthyl) thiocarbamates has also been described[41]. Unfortunately, these conversions are of little use for preparing optically active amines, since the rearrangements occur with very low diastereoselectivities (3—5%)[41].

There are no reported examples of mercury(II) or palladium(II) catalysis of [3,3]-sigmatropic rearrangements of 3-hetero-1,5-dienes. We explored without success the use of mercury(II) trifluoroacetate as a catalyst for the aliphatic Claisen rearrangement and attribute this failure to irreversible binding of the catalyst to the strongly nucleophilic vinyl ether functionality[67].

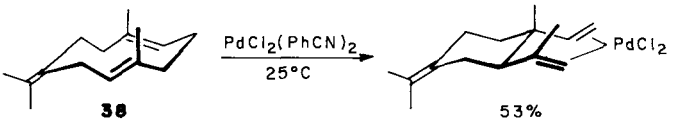
4. Cope Rearrangements

The first example of a metal-promoted Cope rearrangement was reported by *Jonassen* et al.[42], who in 1966 described the preparation of the crystalline palladium(II) chloride complex of *cis*-1,2-divinylcyclohexane **37** from the reaction of excess *cis,trans*-1,5-cyclodecadiene **36** with bis(benzonitrile)palladium(II) chloride (Scheme 9). Reaction of **37** with aqueous potassium cyanide liberated *cis*-



Scheme 9.

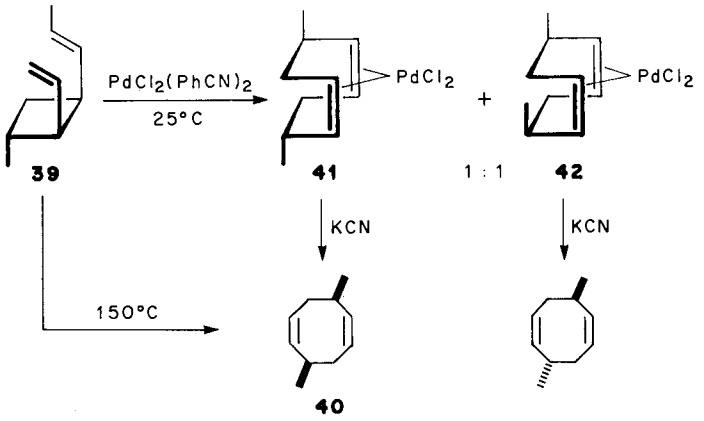
1,2-divinylcyclohexane, the product of thermal Cope rearrangement of **36**. A similar conversion occurred in the presence of sodium hexachloroplatinate, but proceeded much more slowly[42]. The rearrangement of a variety of substituted *cis,trans*-1,5-cyclodecadienes was subsequently studied by *Heimbach* and *Molin*[43]. Mixtures of cyclodecadienes were employed in this study and only solid complexes were isolated, experimental procedures[43] which somewhat complicate the interpretation of the results. Cyclodecadienes **36** with methyl substituents at C-1, C-2, or C-6 did not undergo rearrangements promoted by palladium(II) chloride at 20°C, whereas dienes **36** with substituents at C-3, C-4, C-7, C-8, or C-9 were successfully transformed in the presence of $PdCl_2$[43]. The related transformation of the germacrane **38** (a 1,5-dimethyl-*trans,trans*-1,5-cyclodecadiene) to the palladium(II) chloride complex of the corresponding triene of the elemane structure has also been described (Scheme 10)[44]. In all these cases, the preference for a chair conformation observed for the palladium(II)-promoted rearrangements was identical with that found in the corresponding thermal reactions at elevated temperatures.



Scheme 10.

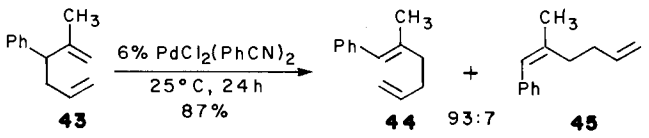
A detailed study of the rearrangement of a variety of *cis*-1,2-divinylcyclobutanes into palladium(II) chloride complexes of *cis,cis*-1,5-cyclooctadienes has also been reported by *Heimbach* and *Molin*[45]. The stereochemistry of the reaction is quite complex and the rearrangements promoted by palladium(II) chloride often occurred with less stereoselectivity than the corresponding thermal rearrangements. For example, thermal rearrangement of **39** gave only cyclooctadiene **40**, while the palladium(II)-induced

reaction afforded nearly equal amounts of the palladium(II) chloride complexes **41** and **42** (Scheme 11)[45].



Scheme 11.

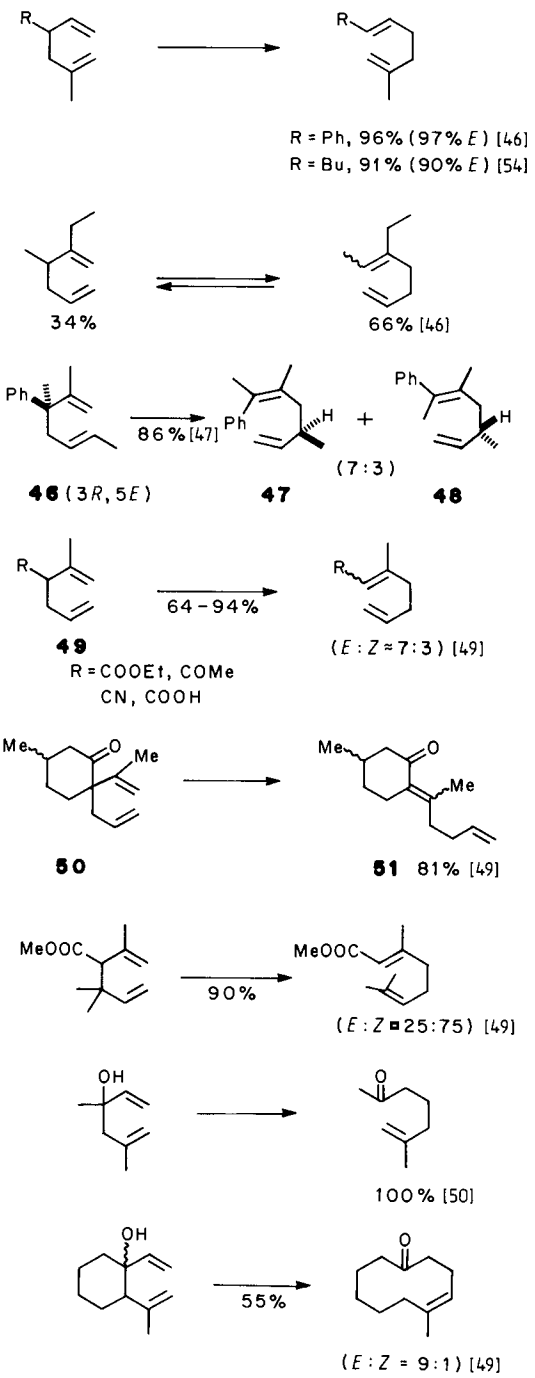
In 1980, *Overman* and *Knoll*[46] reported for the first time that Cope rearrangements could be conducted catalytically using $PdCl_2$ to provide the rearranged diene, rather than the diene-$PdCl_2$ complex. In marked contrast to the facile palladium(II)-catalyzed reaction (Scheme 12), thermal



Scheme 12.

Cope rearrangement of diene **43** required elevated temperatures ($t_{1/2}$ = 13 h at 177 °C) and proceeded much less stereoselectively (**44** and **45** were produced in the ratio 3 : 1). The catalyzed rearrangement of **43** was faster in benzene or dichloromethane than in THF, and a catalytic rate enhancement of 10^{10} (1 M $PdCl_2$) was estimated for the rearrangement of **43** in benzene catalyzed by palladium(II) chloride[46]. Palladium acetate, $Pd(Ph_3)_4$, and mercury(II) trifluoroacetate were not effective catalysts under comparable conditions[46].

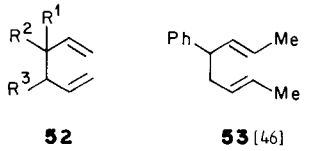
Palladium(II) chloride-catalyzed Cope rearrangements of a representative group of substituted, acyclic 1,5-dienes are shown in Scheme 13. Of particular note is the rearrangement of the optically active diene **46** (99% *ee*) with virtually complete 1,4-transfer of chirality[47]. The observation that only the (2*Z*,5*R*)- and (2*E*,5*S*)-dienes **47** and **48**, respectively, were produced in this rearrangement proves[47] that Cope rearrangements of acyclic dienes catalyzed by palladium(II) chloride occur preferentially with the same chair conformation as thermal Cope rearrangements[47,48]. As the rearrangements of **49** and **50** demonstrate, a number of heteroatom substituents are compatible with this catalytic method[49]. Palladium(II) chloride-catalyzed oxy-Cope rearrangements of tertiary alcohols have also been described[50,51] (see Scheme 13). The advantages of the palladium(II) chloride-catalyzed Cope rearrange-



Scheme 13. Representative examples of palladium(II) chloride-catalyzed Cope rearrangements [a] (at 25–40 °C, molar ratio allylic ester : $PdCl_2(RCN)_2$ = 1 : 0.1).

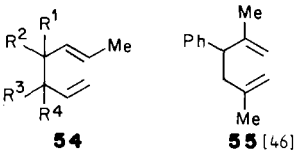
ment are illustrated by the catalyzed rearrangement of diene **50**[49]. Thermal rearrangement of **50** at 220–300 °C gave significant amounts of the β,γ-unsaturated isomer of **51** as well as ene-cyclization products[52].

Unfortunately, the palladium(II) chloride-catalyzed Cope rearrangement has significant limitations. For example, the failure of this catalytic method with substituted 1,5-hexadienes **52**–**55** has been reported by several investigators[46,50,51,53]. Successful palladium(II) catalysis appears to require that the C atoms 2 and 5 of the substituted acyclic 1,5-hexadiene have one hydrogen and one "non-



52 **53** [46]

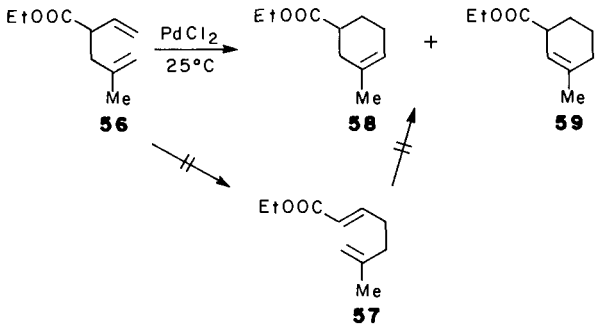
R^1 = Ph [46], OH [50,51]
R^2, R^3 = H, Me



54 **55** [46]

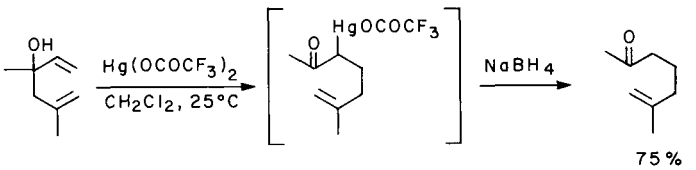
R^1 = Ph [46], OH [51], OMe [51]
R^2, R^3, R^4 = H, Me, Ph

hydrogen" substituent (cf. dienes in Scheme 3 with **52**—**55**)[46]. This feature will be discussed in Section 5. A further limitation is seen in the reaction of diene **56** with palladium(II) chloride, which did not yield the Cope product **57**, but rather cyclohexenes **58** and **59** (Scheme 14)[55].



Scheme 14.

Mercury(II) is much less effective as a Cope rearrangement catalyst than palladium(II) chloride[46]. Nonetheless, a two-step mercury(II)-based method for effecting oxy-Cope rearrangement of tertiary alcohols has been developed by *Gore* et al.[56]. In this approach (see Scheme 15), the diene is treated with mercury(II) trifluoroacetate (molar ratio 1 : 1) at room temperature to yield the rearranged α-mercurated ketone, which is subsequently demercurated with $NaBH_4$[56].

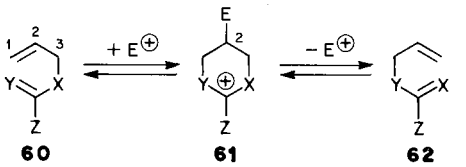


75%

Scheme 15.

5. Cyclization-Induced Rearrangement Catalysis. A Conceptual Model or a Real Mechanism?

Our efforts to develop methods for catalyzing [3,3]-sigmatropic rearrangements have been guided by the mechanistic paradigm we have termed *cyclization-induced rearrangement catalysis* (Scheme 16)[11]. We expected that soft[7] electrophiles would react with molecules such as **60**



60 **61** **62**

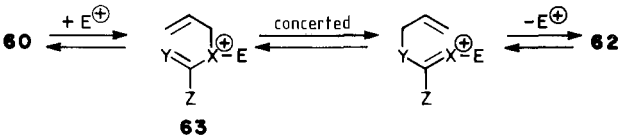
Scheme 16.

at a "soft" carbon-carbon π-bond, rather than a harder heteroatom, and thus promote a polyene-like cyclization[57] to yield **61**[58] (or a nucleophile-trapped equivalent). Alternative Grob-type fragmentation[59] of **61** would afford the rearranged product **62**. For catalysis of this type to be effective, both the cyclization and fragmentation steps have to be rapid, and the cyclic intermediate must be less stable than **60** and **62**. At the time our work began, ample indications existed in the literature that mercury(II)[60] and palladium(II)[61] salts rapidly and reversibly promoted the addition of a variety of nucleophiles to carbon-carbon double bonds. To our knowledge, a cyclization-induced rearrangement mechanism was first suggested by *Henry*[23] for intramolecular allylic ester rearrangements catalyzed by palladium acetate (see Scheme 5).

The present article illustrates that Hg^{II} and Pd^{II} salts are able to catalyze a wide variety of [3,3]-sigmatropic rearrangements involving the making and breaking of C—O, C—N, C—S, and C—C bonds. These diverse, catalyzed transformations show a remarkable number of similarities, and it is appropriate to briefly consider whether or not a cyclization-induced rearrangement mechanism is, in fact, a proper mechanistic description of *all* these catalyzed reactions.

For the Hg^{II}- and Pd^{II}-catalyzed allylic ester and hetero-Cope rearrangements there is ample evidence to preclude mechanisms involving allyl cation or η^3-allylpalladium intermediates. In all cases studied, the catalyzed transformations proceed without scrambling of the allyl fragments (i.e. no competing [1,3]-shifts) and with clean suprafacial stereochemistry. In contrast, several related reactions which are catalyzed by palladium(0) and probably involve η^3-allyl intermediates do *not* show similar clean regio-[8d,e,29] or stereochemical control[8b].

Mechanistically, a cyclization-induced rearrangement (Scheme 16) or concerted charge-induced rearrangement[6,62] (Scheme 17) would be consistent with these observations. Both mechanisms involve intramolecular reorganization of a catalyst-substrate complex and thus could exhibit stereo- and regioselectivities similar to an intramo-



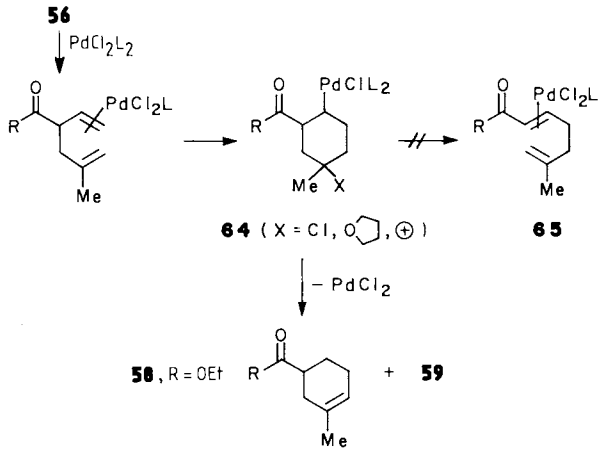
63

Scheme 17.

lecular thermal rearrangement. There is strong evidence, primarily from *Schmid*'s group[62] that acid-catalyzed, aromatic Claisen and amino-Claisen rearrangements occur via charge-induced rearrangement pathways. However, the evidence accumulated to date is quite persuasive in favoring a cyclization-induced rearrangement mechanism for mercury(II)- and palladium(II)-catalyzed allylic ester and hetero-Cope rearrangements. Some of the key observations are: 1) the soft electrophiles[7] mercury(II) and palladium(II) are much more effective than hard Lewis or Brønsted acids in catalyzing the rearrangement of allylic imidates and allylic esters[11,37]; 2) the general requirement[10,11,21,28,40] that substrates **60** have a H atom at C-2 is consistent with the bonding of a bulky metal at this carbon. Alkyl substitution at this site should not dramatically decrease[3d,63] the rate of a concerted [3,3]-sigmatropic rearrangement of complex **63**; 3) intermediate **61** rationalizes the rate of rearrangement of allylic esters in both mercury(II)-catalyzed ($Z = NR_2 > 4$-methoxyphenyl $> CH_3$)[10-12] and palladium(II)-catalyzed ($Z = NR_2 > OR > CH_3 > CF_3$)[21,28] reactions, since these relative rates directly parallel the stability of carbocation **61**.

The mechanistic picture is less clear for $PdCl_2$-catalyzed Cope rearrangements. In particular, the reactivity patterns observed for cyclic and acyclic 1,5-dienes are quite different. Thus, $PdCl_2$-catalyzed Cope rearrangements of acyclic dienes require[46,49-51] an alkyl substituent at C-2 (or C-5). On the other hand, 2-methyl-*cis,trans*-1,5-cyclodecadiene apparently does not rearrange[43] in the presence of $PdCl_2$, while *cis,trans*-1,5-cyclodecadiene does[42,43]. The palladium(II)-catalyzed rearrangements of *cis*-1,2-divinylcyclobutanes are different still, since products other than those of the thermal Cope reaction are sometimes obtained[45]. Transformations of *cis*-1,2-divinylcyclobutanes may be considered special cases due to the strain of the four-membered ring and the enforced boat conformation of intermediates or transition states whose formation involves bond-formation concerted with (or prior to) bond cleavage. However, the significance of the apparent differences between the rearrangements of substituted *cis,trans*-1,5-cyclodecadienes and substituted acyclic 1,5-dienes is unclear at present.

The evidence available to date on $PdCl_2$-catalyzed Cope rearrangements of acyclic 1,5-dienes is compatible[47,58] with a cyclization-induced rearrangement mechanism[64]. In particular, the requirement[46,49-51] for one "non-hydrogen" substituent at C-2 or C-5 of a 1,5-hexadiene is rationalized by the importance of this group (Z in **61**) in stabilizing the positive charge developed in the cyclization step. The failure of the 2,5-disubstituted hexadiene **55** to rearrange would then reflect the difficulties in forming a bond between the bulky metal catalyst and a sterically hindered tertiary carbon. Since a cyclohexyl intermediate is the key feature[58] of a cyclization-induced rearrangement mechanism, the many examples[55,65] of palladium(II)-promoted cyclizations of 1,5-dienes to form six-membered ring products provide further support for this mechanism. For example, the formation of cyclohexenes from the reaction of diene **56** with $PdCl_2$ (Scheme 14) is best interpreted as a "trapping" of cyclic intermediate **64** (Scheme 18), although the mechanistic details for the conversion of **64** into the cyclohexene product are currently unclear. Fragmentation of **64** to alkenepalladium(II) complex **65** is presumably not favored in this case because of the relative instability[66] of $PdCl_2$-complexes of electron deficient alkenes.



Scheme 18.

6. Conclusion and Outlook

Mercury(II) and palladium(II) salts have broad applications for the catalysis of [3,3]-sigmatropic rearrangements. The accelerations in rate brought about are dramatic: 10^{10}- to 10^{14}-fold for a 1 M solution of the catalyst. Catalytic effects of this magnitude allow many previously difficult transformations to be conducted at or near room temperature, often with attendant increases in stereoselectivity and decreases in formation of by-products. Perhaps of greater significance is that these compounds can be used to catalyze [3,3]-sigmatropic rearrangements which have no useful thermal counterparts. Salts of mercury(II) and palladium(II) tolerate a wide variety of functionalities, with the important exception of groups which bind these soft metal salts tightly. Of particular significance is that catalysis of a large number of diverse [3,3]-sigmatropic rearrangements which form a variety of C–X bonds (C–O, C–N, C–S, C–C) has already been demonstrated. It seems likely that in the future many additional applications will appear.

The concept of cyclization-induced, rearrangement catalysis has served well as a framework for our studies. Although some important mechanistic questions remain unanswered, particularly with regard to $PdCl_2$-catalysis of Cope rearrangements, there is now a considerable body of evidence to support the cyclization-induced rearrangement mechanism for many mercury(II)- and palladium(II)-catalyzed [3,3]-sigmatropic rearrangements.

The results described in this article from this laboratory were, to a large extent, the work of four talented doctorate students: Curtis Campbell, Fredrick Knoll, E. Jon Jacobsen, and Alfred Renaldo. Our efforts in the area of catalysis have been supported from their inception by grants from the U.S. National Science Foundation, with additional assistance being provided by the Camille and Henry Dreyfus Foundation.

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[1] This nomenclature [2] refers to the overall bonding changes which occur in a rearrangement and implies nothing about the *mechanism* of the process. Although the sigmatropic rearrangement nomenclature was originally used by *Woodward* and *Hoffmann* for "uncatalyzed intramolecular process" [2], it has been widely employed in recent years to characterize reactions which are not of this mechanistic type. We feel the term is now best used in a non-mechanistic sense.

[2] R. B. Woodward, R. Hoffmann: *The Conservation of Orbital Symmetry*, Verlag Chemie, Weinheim 1970, chapt. 7.

[3] Reviews of selected [3,3]-sigmatropic rearrangements: a) G. B. Bennett, *Synthesis 1977*, 589; b) T. Hayashi, *Yuki Gosei Kagaku Kyokai Shi 34* (1976) 396; c) A. Jefferson, F. Scheinmann, *Q. Rev. Chem. Soc. 22* (1968) 391; d) S. J. Rhoads, N. R. Raulins, *Org. React. 22* (1975) 1; e) L. E. Overman, *Acc. Chem. Res. 13* (1980) 218; f) E. Winterfeldt, *Fortschr. Chem. Forsch. 16* (1971) 75; g) F. E. Ziegler, Acc. Chem. Res. 10 (1977) 227.

[4] W. von E. Doering, W. R. Roth, *Tetrahedron 18* (1962) 67; R. K. Hill, N. W. Gilman, *Chem. Commun. 1967*, 619; H.-J. Hansen, H. Schmid, *Tetrahedron 30* (1969) 1959.

[5] Many of these reactions are not catalytic and employ stoichiometric amounts of the "catalyst". Such reactions are best described as induced or promoted by the reagent.

[6] R. P. Lutz, *Chem. Rev. 1984*, in press.

[7] R. G. Pearson: *Hard and Soft Acids and Bases*, Dowden, Hutchinson and Ross, Stroudsburg, PA, 1973.

[8] See e.g.: a) J. Tsuji, I. Minami, I. Shimizu, *Tetrahedron Lett. 24* (1983) 1793; b) B. M. Trost, T. A. Runge, *J. Am. Chem. Soc. 103* (1981) 7559; B. M. Trost, E. Keinan, *J. Org. Chem. 44* (1979) 3451; B. M. Trost, T. R. Verhoeven, J. M. Fortunak, *Tetrahedron Lett. 1979*, 2301; c) T. Mandai, K. Hara, M. Kawada, J. Nokami, *ibid. 24* (1983) 1517; d) Y. Tamaru, Z. Yoshida, Y. Yamada, K. Mukai, H. Yoshioka, *J. Org. Chem. 48* (1983) 1293; e) Y. Yamada, Y. Mukai, H. Yoshioka, Y. Tamura, Z. Yoshida, *Tetrahedron Lett. 1979*, 5015; f) L. V. Dunkerton, K. T. Brady, F. Mohamed, *ibid. 23* (1982) 599.

[9] These rearrangements are believed to typically involve η^3-allylpalladium(II) intermediates [8] and often exhibit reactivity patterns and regio- and stereoselectivities quite different from the corresponding Hg^{II}- or Pd^{II}-catalyzed transformations.

[10] L. E. Overman, C. B. Campbell, *J. Org. Chem. 41* (1976) 3338.

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[58] Clearly, the reaction **60** → **62** could involve other intermediates. However, the formation at some point on the reaction pathway of the σ-bonded cyclic intermediate **61** is the key feature of this mechanism. For example, in the $PdCl_2$-catalyzed Cope rearrangement, intermediate **61** could be reached by a two-step process involving initial bond formation between Y and Pd^{2+} followed by insertion of the 1,2-π bond into the PdY σ bond. This mechanism has been suggested by *P. M. Henry*, personal communication.

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Carbene Complexes in Organic Synthesis

New Synthetic Methods (47)

By Karl Heinz Dötz*

Transition metals are finding increasing use in organic synthesis on the borderline between "organic" and "inorganic" chemistry. Advantage is taken thereby of the fact that metal-induced CC bond formation often takes place with remarkable selectivity. The rapid development that has taken place in this area of chemistry is clearly demonstrated by the carbene complexes, examples of which are now known for almost all transition elements, and which have transformed from organometallic curiosities into synthetically useful reagents in less than two decades since the first studies of *E. O. Fischer*. They are not only suitable as carbene-transfer agents but also undergo interesting cycloadditions with other ligands in the co-ligand sphere. Their manipulation requires techniques no more complicated than those for Grignard reactions. Thus, carbene complexes can also be used in the synthesis of natural products such as vitamins or antibiotics.

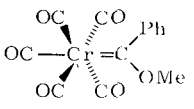
1. Preliminary Remarks

One of the most outstanding properties of transition metals is their ability to stabilize short-lived molecules as ligands in coordination compounds. There are two advantages to this: Firstly, a reactive molecule can be studied and characterized as the ligand of a complex that is much more easily handled. This will especially appeal to the chemist who is interested in mechanism, spectroscopy, and structure. Secondly, the metal fragment can also be considered as a protecting group, which can be cleaved off when so desired. If the complex can be "bottled" and stored, it offers the synthetically oriented chemist a source of short-lived molecules that can be tapped at any time. The easier the complex is to prepare, the more likely it will be used.

Carbenes—derivatives of divalent carbon—are a widely used building block in organic synthesis[1]. In particular, they are used in the synthesis of small rings. Classical sources of carbenes are diazo compounds and ketenes[2–4], which readily undergo thermal, photochemical, or metal-induced cleavage. In addition, organometallic precursors such as trihalomethylmercury compounds[5] and α-haloalkyllithium compounds[6] have also proven useful. The reactivity of the carbene species is dependent on both the choice of precursor and the method of generation. Truly free carbenes are only to be expected in gas-phase reactions; for example, by thermolysis or photolysis of ketenes. In contrast, one must reckon in solution with a broad spectrum of more or less stabilized carbene species, the reactive behavior of which can only be vaguely defined by the term "carbenoids".

2. Carbene Complexes—Classification and Pattern of Reactivity

Carbene complexes contain metal-stabilized carbenes[7]. These compounds can be divided into two classes: the "Fischer-type"[8] and the "Schrock-type"[9], named after their discoverers. Subdivision into "carbene complexes" and "alkylidene complexes", which is encountered now and then, makes little sense didactically and has at most only historical significance.



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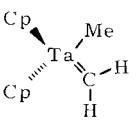
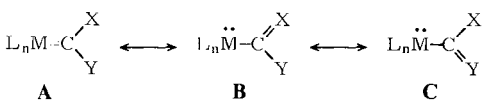


2

"Fischer-type" compounds such as **1** contain a metal from Groups VI to VIII. It is present in a low oxidation state, which is stabilized by a series of other ligands with pronounced acceptor properties (e.g., carbon monoxide). A typical representative is pentacarbonyl[methoxy(phenyl)carbene]chromium **1**, the first carbene complex that was characterized by X-ray crystallography[10]. The carbene carbon in this compound is considered to be sp^2-hybridized; the distances between it and its substituents, especially the heteroatoms, are short relative to single bonds. The bonding must therefore be described by the three resonance structures **A**—**C**, the relative importance of which may differ in individual cases. For reasons of graphic depiction, exclusively resonance structure **A** will be used in the following discussion.



A **B** **C**

Complexes of the "Schrock-type" such as **2** (Cp = cyclopentadienyl) are characterized by an early transition metal.

The reactive behavior of the "Fischer" carbene complexes is illustrated by **3** in Scheme 1[11]. Characteristic is the electrophilicity of the carbene carbon atom, which, therefore, is the preferred site of attack for nucleophilic

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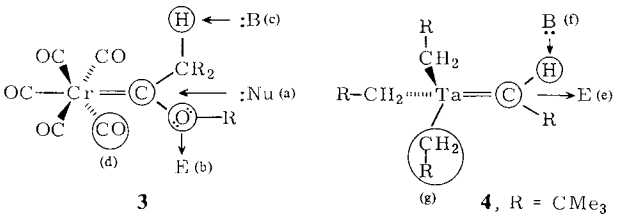
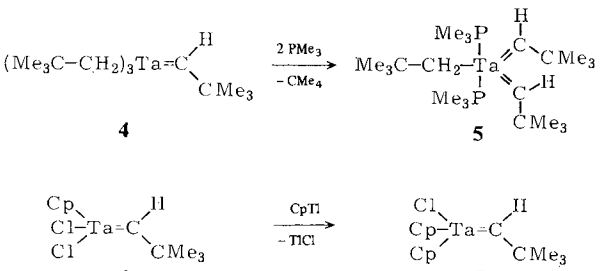
reagents :Nu [route (a)]. In contrast, electrophiles E are coordinated to the carbene heteroatom [route (b)]. This offers an easy access to carbyne complexes[7, 12]. The acidity of the C–H groups in the α-position of the carbene ligand offers a further reaction possibility. Thus, alkylcarbene complexes are deprotonated by bases :B and converted into carbenemetal anions, which can undergo bond formation with a series of electrophiles [route (c)]. Finally, as is known from the chemistry of carbonylmetal compounds, other ligands can be substituted for carbon monoxide [route (d)].



3 **4**, R = CMe_3

Scheme 1. Pattern of reactivity of "Fischer" and "Schrock" carbene complexes **3** and **4**, respectively. (a)–(g), see text.

The polarity of the metal-carbon bond is reversed in going from the "Fischer" carbene complexes **3** to the "Schrock"-type compounds **4** (Scheme 1)[9]. Consistent with a charge distribution $\overset{\delta\oplus}{M}-\overset{\delta\ominus}{C}$, electrophiles add to the carbon [route (e)]. Likewise, strong bases result in deprotonation; thus, this takes place in the neopentylidene ligand of **4** directly on the metal-coordinated carbon [route (f)]. Reactions in the co-ligand sphere show clearly that the number of valence electrons of the metal can vary widely: For example, reaction of **4** with trimethylphosphane and of **6** with thallium cyclopentadienide take place with retention of the alkylidenemetal structure to give compounds **5** and **7**, respectively [route (g)]. Compounds **5** and **4**, in which the central metal atom has 14 and 10 valence electrons, respectively, contrast with the 18-electron complex **2**.



4 **5**

6 **7**

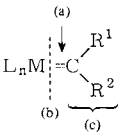
In addition to the complexes with terminal carbene ligands, alkylidene-bridged binuclear complexes have recently become known, especially through the studies of *Herrmann*. These compounds, as well as metal-coordinated vinylidenes and propadienylidenes, will not be dealt with in the following discussion since these classes of compounds have recently been reviewed elsewhere in the literature[13, 14].

3. Synthesis and Functionalization of the Carbene Ligand

3.1. Strategies for the Synthesis of Carbene Complexes

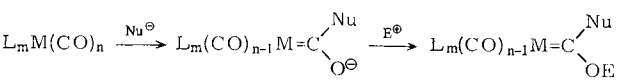
Since the first directed synthesis of a stable carbene complex by *Fischer* and *Maasböl*[15] in 1964, a large number of methods have been developed, providing access to several hundred compounds involving nearly all the transition metals. The rapid expansion of this area of research is reflected in a series of recent comprehensive reviews[7, 16–18]. Therefore, only a few characteristic synthetic examples will be selected here from the abundance of material available. Basically, three strategies are used for the preparation of carbene complexes (Scheme 2):

a) The transformation of a metal-carbon bond that is already present,
b) the addition of a carbene precursor to a coordinatively unsaturated metal complex, and
c) the modification of a carbene complex that is already available.



Scheme 2. Strategies for the synthesis of carbene complexes. (a)–(c), see text.

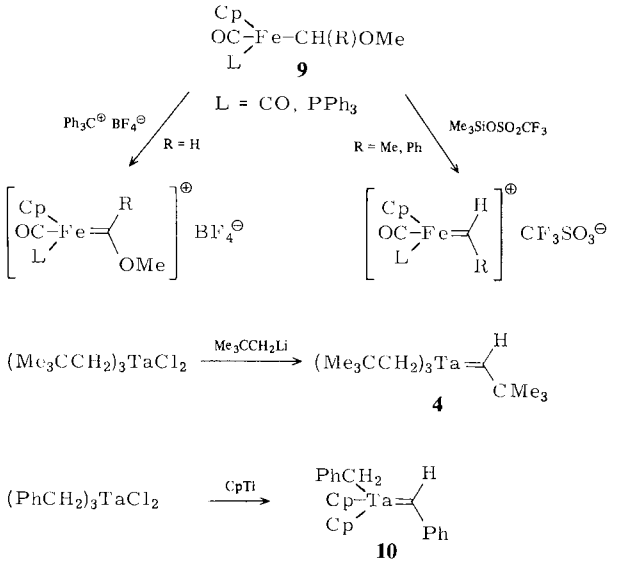
Route (a) has the greatest potential, in particular, because the commercially available carbonylmetal compounds can be used as starting materials. In this method a carbonyl ligand is converted into an alkoxy- or aryloxycarbene ligand by successive addition of a nucleophile and an electrophile. Organolithium compounds have proven to be especially useful as nucleophiles. Even at low temperatures they add rapidly enough and are preferred to the Grignard reagents[19], both for this reason and because of better yields. The rate of addition depends on the electrophilicity of the carbonyl carbon and on steric factors, which are determined by the number and kind of co-ligands. Thus, methyllithium reacts with $W(CO)_6$ about 230 times faster than with $(CO)_5WP(OPh)_3$, about 380 times faster than with $(CO)_5W(PPh_3)$, and about 660 times faster than with $(CO)_5WP(c\text{-}C_6H_{11})_3$[20]. The acyl metallates **8** are preferably alkylated with oxonium salts or fluoroalkanesulfonates; as a rule, the neutral carbene complexes are formed in 70–90% yields[21].



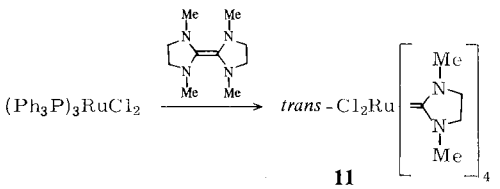
8

Besides additions to ligands, the elimination of substituents from the α-position of alkyl ligands also leads to carbene complexes. In the carbonyl(cyclopentadienyl)iron complexes **9**, a hydride or a methoxy substituent is eliminated by trityl tetrafluoroborate or trimethylsilyl trifluoro-

methanesulfonate, respectively[22,23]. The synthesis of "Schrock-type" compounds is based on the elimination of an α-hydrogen from neopentyl and other similar ligand systems[9]. Steric overcrowding of the ligand sphere is considered to be the driving force for the formation of the alkylidene complexes **4** and **10**. The stability of these compounds is therefore also increased by the introduction of cyclopentadienyl ligands.



The preparation of carbene complexes from carbene precursors has so far mainly been applied to diazo compounds[24] and electron-rich alkenes[25]. By cleavage of tetraaminoethene derivatives, several carbene ligands can be coordinated to a metal, as in **11**[26].

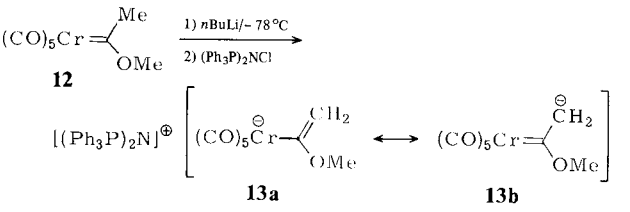


3.2. Functionalization of the Carbene Ligand

The metal-carbene bond is usually stable enough to permit a subsequent functionalization within the carbene ligand. To that end, deprotonation reactions as well as addition reactions have been applied to the series of carbonyl-carbene complexes.

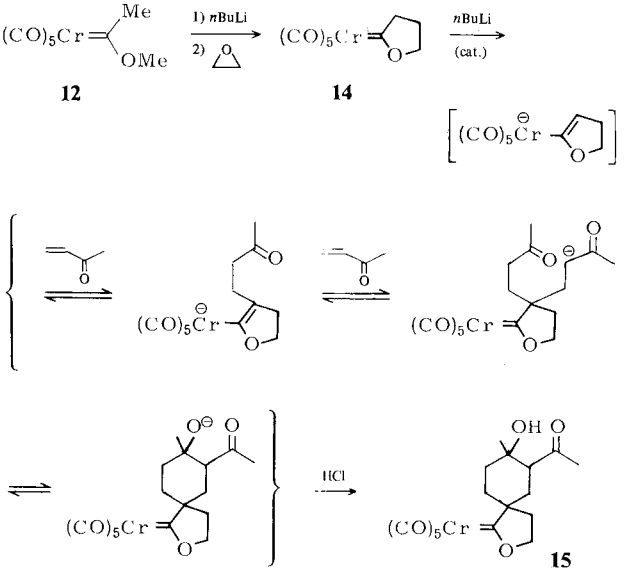
3.2.1. Carbene-Complex Anions

Complexes whose carbene substituents have hydrogen atoms in the α-position show considerable acidity[27]. Thus, pentacarbonyl[methoxy(methyl)carbene]chromium **12** has a pK_a value of ≈8[28]. The conjugate base obtained by deprotonation, which can be isolated as the bis(triphenylphosphoranediyl)ammonium salt, is, according to spectroscopic findings, better regarded as the vinylchromium anion **13a** than as carbanion **13b**.



The reaction of carbene-complex anions with electrophiles is frequently used for C–C bond formation. The anions are smoothly alkylated with allyl and benzyl bromides, α-bromo esters, aldehydes, and α,β-unsaturated carbonyl compounds[29–31]. Dialkylation as well as monoalkylation can occur[31,32], the degree of alkylation being controlled by the use of stoichiometric or catalytic amounts of base. This is illustrated by the example in Scheme 3.

The tetrahydro-2-furylidene ligand in **14** is synthesized by nucleophilic ring opening of oxirane with the anion **13**, which is generated from the carbene complex **12** using stoichiometric amounts of *n*-butyllithium[31]. It can be further functionalized in the presence of methyl vinyl ketone and a catalytic amount of base to give the spirocyclic system **15**[33].

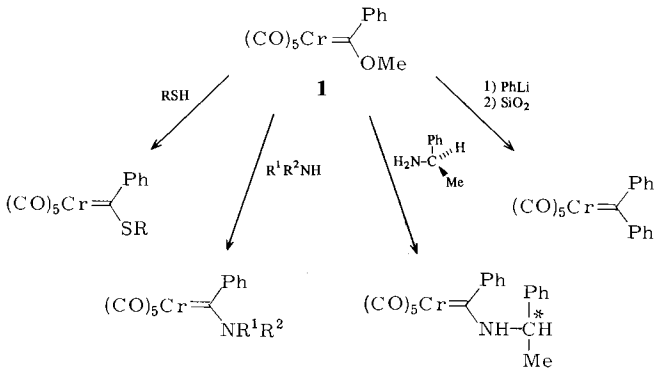


Scheme 3. Functionalization of carbene ligands via carbene-complex anions.

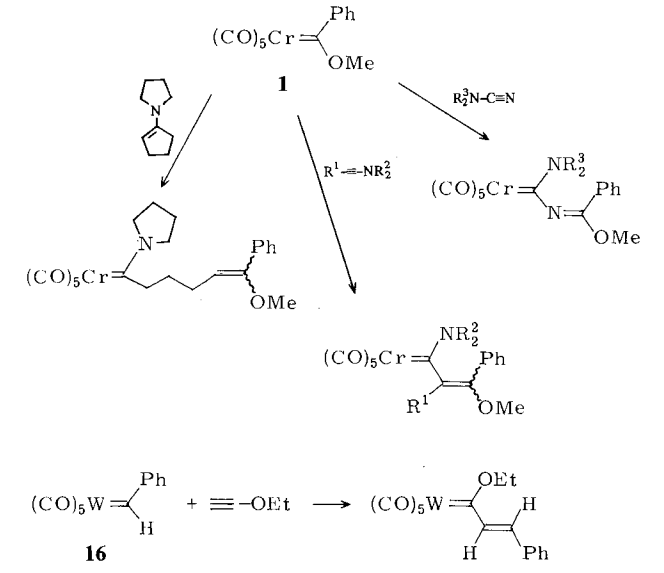
3.2.2. Addition to Carbene Ligands

Mulliken population analyses[34,35] and ESCA studies[36] have shown for "Fischer"-type compounds that the carbon atom in the carbonyl ligand bears a larger positive charge than the carbene carbon. In contrast, extensive experimental evidence confirms that the addition of nucleophiles takes place at the carbene carbon. Apparently, the course of these reactions is not charge-controlled but rather orbital-controlled. Thus, MO calculations on methoxy(methyl)carbene complex **12** show that the lowest unoccupied molecular orbital (LUMO) is spatially and energetically localized mostly on the carbene carbon atom[34]. The nucleo-

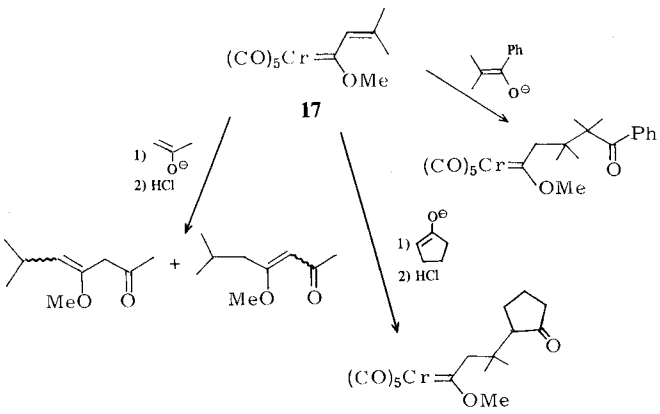
philic addition at the carbene carbon has found wide application in the modification of carbene ligands; the alkoxycarbene complexes, which are obtainable directly from the carbonylmetal compounds, function as intermediates. Thiols[37], primary and secondary amines[38], and aryllithium compounds[39,40] react by substituting for the methoxy group, leading to alkyl- (or aryl)thio-, amino- and arylcarbene ligands, respectively. The mechanism of the aminolysis of alkoxycarbene complexes is similar to that of the aminolysis of esters[41]. By using chiral amines, the reaction can be exploited for the synthesis of optically active carbene complexes[42,43]. These examples show that alkoxycarbene complexes can thus be regarded as organometallic ester equivalents.



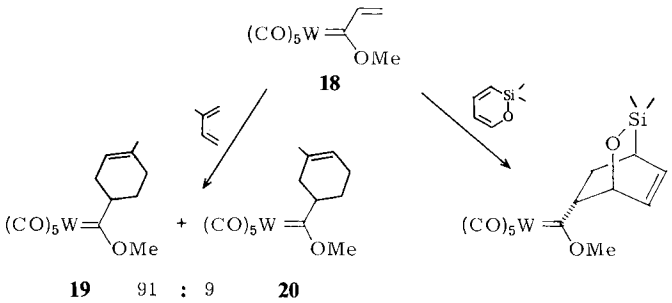
In nucleophilic multiple bond systems, not only the primary addition but also an insertion into the metal-carbene bond takes place. Enamines, ynamines, and cyanamides react smoothly with alkoxycarbenes of type **1**[44–47], whereas ynyl ethers require that the carbene carbon be more electrophilic, as is the case for the thermally labile benzylidene compound **16**[48]. The formation of the CC double bond always takes place stereospecifically to give predominantly or even exclusively the *E*-configuration.



In the case of vinylcarbene complexes **17**, direct attack at the carbene carbon atom competes with a conjugate addition to the olefinic double bond[49,50]. In the process, steric factors play a role, as shown by the example of enolate addition: the less bulky enolate of acetone attacks the carbene carbon atom. Decomposition of the addition product leads to a mixture of isomeric enones. In contrast, the more bulky enolates of cyclopentanone and isobutyrophenone are added at the terminal vinyl position.



Vinylcarbene ligands behave as dienophiles in the sense of a Diels-Alder reaction. The cycloaddition of **18** with isoprene is superior in terms of yield to the $AlCl_3$-catalyzed reaction of the ester analog methyl acrylate—the regioselectivities and reaction rates being comparable[51]. The method is also suitable for the synthesis of bicyclic systems.



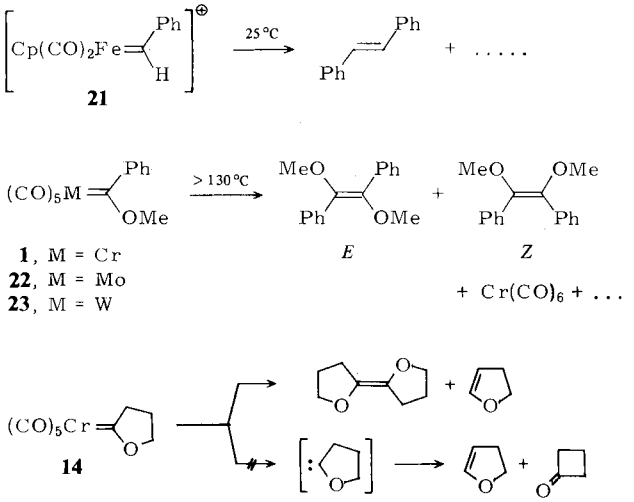
4. Carbene-Transfer Reactions

For some time it remained an open question whether the cleavage of the metal-carbene bond resulted in "free" carbenes. Although numerous different preparative methods have been used for the release or transfer of the carbene ligand, there has so far been no evidence for the appearance of a "free" carbene. In contrast, the influence of the metal on the product distribution has often been demonstrated.

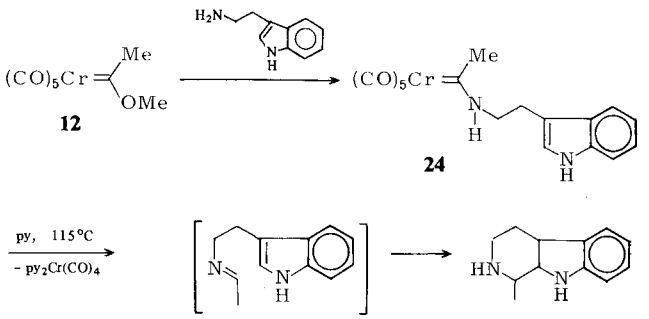
4.1. Cleavage of the Metal-Carbene Bond

The thermal decomposition of carbene complexes usually results in dimerization of the carbene ligand[52,53]. As expected, the cleavage of the metal-carbene bond is facilitated by the absence of stabilizing heteroatoms in the carbene ligand. Thus, the benzylidene ligand in the iron

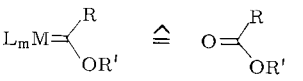
complex **21** already dimerizes at room temperature[54]. In contrast, the cleavage of the α-methoxybenzylidene ligand in **1**, **22** and **23** only begins above 130°C[52,55]. The elimination of carbon monoxide proved to be the initial step of the reaction. The metal must be involved in the formation of the C=C bond, as shown by the change in *E/Z* ratio within the series chromium, molybdenum, and tungsten. The thermolysis of the cyclic carbene complex **14** leads to a similar result: the reaction mixture contains no cyclobutanone, which is known to be a characteristic stable rearrangement product of metal-free 2-tetrahydrofurylidene[56].



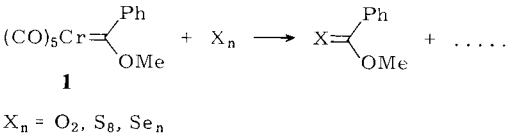
Ligand substitution is a more gentle method of cleaving the metal-carbene bond. Carbon monoxide[38], tertiary phosphanes[57,58], and amines[53,59] are suitable as substituting ligands. When using amines, the acidity of carbene complexes must be taken into account. Alkylcarbene ligands do not dimerize: instead, a base-induced 1,2-hydrogen shift takes place, which can be exploited for the preparation of enol ethers and azomethines. A reaction in the alkaloid series serves as example: the methoxy compound **12** is converted into the aminocarbene complex **24** by aminolysis with tryptamine. Subsequent cleavage of the carbene ligand in pyridine affords tetrahydroharmane in 17% yield[60].



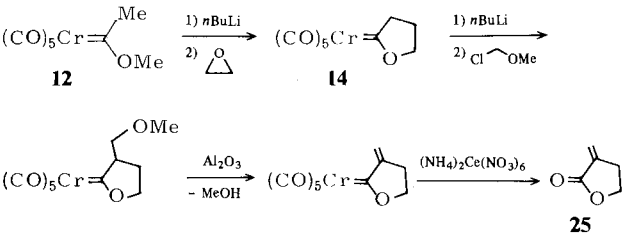
As shown by their aminolysis, alkoxycarbene complexes can be regarded as ester equivalents, the metal fragment corresponding to the carbonyl oxygen:



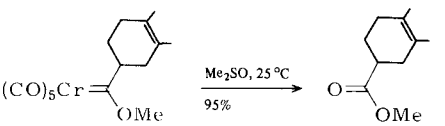
This analogy suggests the possibility of an oxidative cleavage of the metal-carbene bond. In early studies, oxygen was used directly as the oxidizing agent[61]. However, since it is not a clean reaction, the method has not achieved preparative significance. Nevertheless, it can be used for the preparation of difficultly obtainable thio or seleno esters, using sulfur or selenium as oxidizing agents[62].



Cerium(IV) compounds are versatile reagents for the transformation of carbene ligands into carbonyl compounds[29,63]. The oxidation does not affect multiple bonds and generally proceeds in high yield, so that it is also suitable for the characterization of carbene ligands in labile complexes. An example of its preparative use is the synthesis of the α-methylene-γ-butyrolactone skeleton **25**, which is a component of several natural products and has been synthesized via **14** in an overall yield of 20% from the methoxy(methyl)carbene ligand bonded to the chromium center of **12**[64].



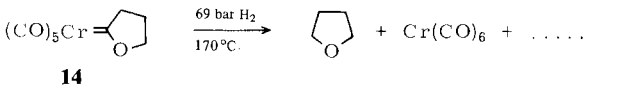
Mild reaction conditions during the oxidation are ensured using dipolar reagents such as amine oxides, sulfoxides, thioamide *S*-oxides, or iodosylbenzene[51,65,66], of which especially the use of dimethyl sulfoxide has become established.



In contrast to the oxidation, the reductive cleavage of the metal-carbene bond has achieved no preparative significance.

Hydrides reduce carbene complexes merely to alkylmetal compounds[67]. The cleavage of the carbene ligand with hydrogen, resulting in formation of the saturated hydrocarbon, requires drastic conditions. In order to suppress competing carbene dimerization, low concentrations of the

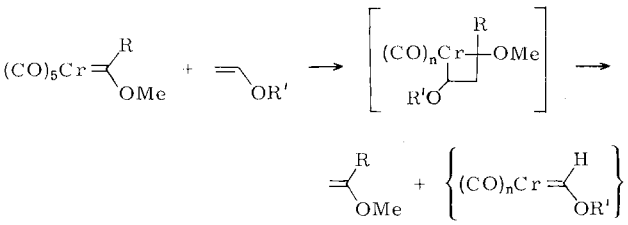
carbene complex, as well as relatively high hydrogen pressure, have to be used[51,68].



14

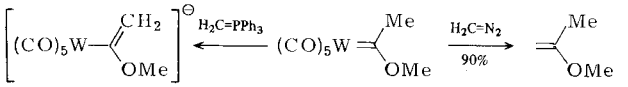
4.2. Alkenylation Reactions

Carbene (alkylidene) ligands can be used for the synthesis of olefinic double bonds. Thus, the electrophilic carbene carbon of "Fischer" complexes reacts with nucleophilic multiple bond systems such as enol ethers, enamines, diazoalkanes, or phosphorus ylides to give alkenes[69–73]. This type of reaction is a model for the metathesis of olefins (Section 7.1). Four-membered metallacycles are assumed to be intermediates, the cleavage of which affords, in addition to the olefin **26**, a coordinatively unsaturated carbene-complex species.

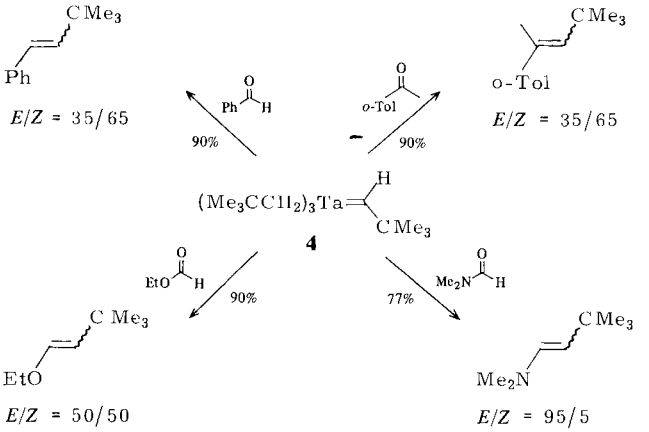


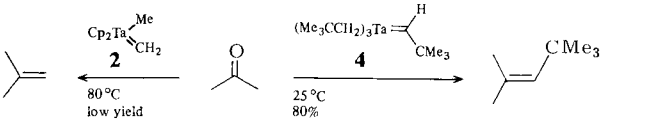
26

The alkenylation of the carbene ligand is dependent on the steric demands as well as on the basicity of the nucleophile. Thus, in contrast to ethylidene(triphenyl)phosphorane, the bulkier isopropylidene compound no longer undergoes C=C bond formation. For alkylcarbene complexes, phosphorus ylides effect a competing deprotonation, hence it is better to resort to the less basic diazoalkanes.

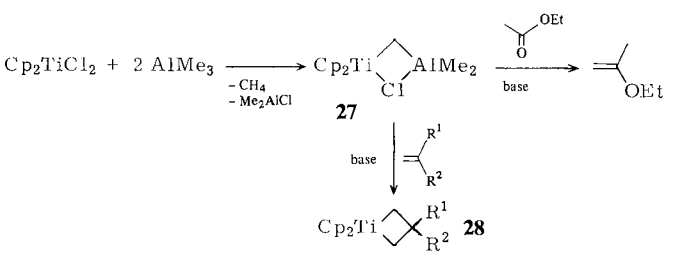


"Schrock"-type complexes which contain an early transition metal can be regarded as transition-metal analogs of ylides as far as their reaction behavior is concerned[9]. Accordingly, they react with carbonyl compounds in Wittig-type reactions to form C=C bonds. Thus, the tantalum-neopentylidene complex **4** converts ketones and aldehydes into *tert*-butyl-substituted olefins. The metal forms an oxo compound, which presumably is polymeric. Of great preparative significance is the discovery that these complexes—in contrast to the phosphorus ylides[74]—also alkenylate esters and even amides[75]. The reason for this is to be seen in the pronounced oxophilicity of the early transition elements. The rate of alkylidene transfer is determined not only by steric factors in the electrophile (acetophenone reacts immediately at room temperature, pivaldehyde only very slowly over several hours), but also by the electronic configuration of the metal. The 18-electron complex **2** reacts with acetone to give only small amounts of isobutylene, whereas the 10-electron compound **4** gives the corresponding olefin in 80% yield. This result supports the assumption that coordination of the carbonyl carbon to the metal precedes transfer of the alkylidene ligand.

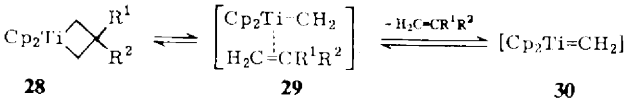




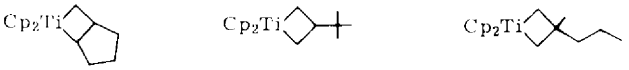
Compounds of titanium are especially suitable for the transfer of methylene. Starting from dicyclopentadienyltitanium dichloride and trimethylaluminum, a titanium-methylene complex is obtained that is stabilized as the Me_2AlCl-adduct **27** ("Tebbe compound")[76]. Although this species can be used directly for methylene transfer, for example, for conversion of ethyl acetate into ethyl isopropenyl ether[76], an indirect route via the titanacyclobutane intermediate **28** has proven to be advantageous. This compound is obtainable from **27** and an olefin and—in contrast to the aluminum reagent—can even be handled as a solid for a short time in air[77–79].



Labeling experiments and kinetic studies suggest that the titanacyclobutane can be cleaved to the alkene-methylene complex **29** and thus can be used as a source of dicyclopentadienyl(methylene)titanium **30**[79,80]. The thermal stability of the metallacycle **28** depends on the substituents. Bicyclic or sterically-shielded systems such as **28a** or **28b** are relatively stable (up to ca. 50—60°C); the methylene complex **30** is released from the most widely used dialkyl derivative **28c** at 0°C and from the aluminum reagent **27** even above −40°C[81].

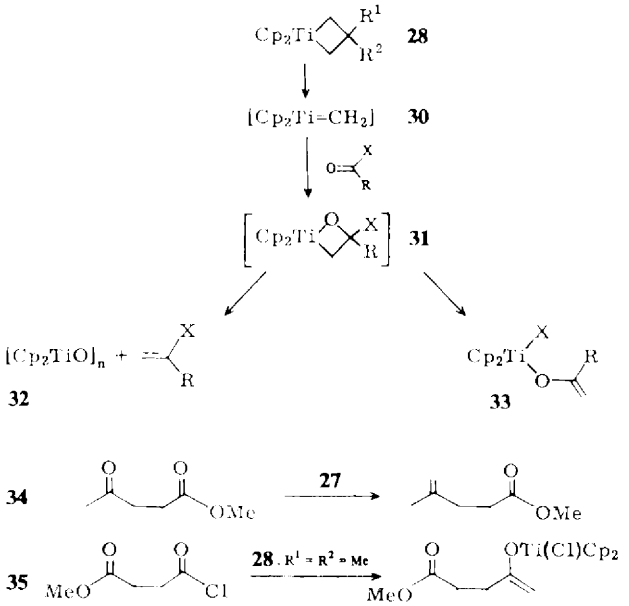


28 29 30



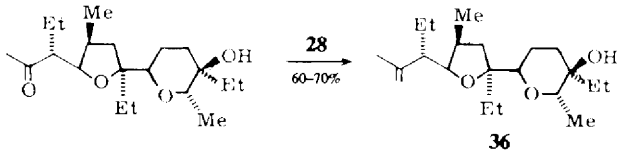
28a 28b 28c

The reaction of the titanacycles with carbonyl compounds can proceed by two pathways. An oxametallacycle **31** is assumed to be a common intermediate, which can be cleaved to give the olefin. The formation of the oxatitanocene **32** is regarded as the driving force for this cleavage. In this way, aldehydes, ketones, esters, and amides can be converted into the corresponding alkenes[79,82]. However, if the carbonyl component contains a good leaving group, as, for example, in acid chlorides or anhydrides, then the titanium enolate **33** is formed by migration of this group to the metal[83,84]. Competition experiments using 1,4-dicarbonyl compounds show considerable regioselectivity. Thus, methylene transfer decreases along the series ketone > acid chloride > ester.



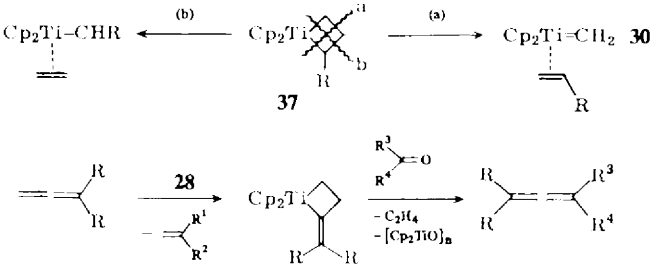
28 30 31 32 33 34 35

The titanacyclobutanes **28** enable an alkylidene transfer under non-basic conditions. They are thus suitable for reactions with enolizable ketones, there being no danger of racemization of asymmetric centers, and are therefore a good complement to the phosphorus ylides. Their synthetic use is illustrated by a step in the synthesis of Lasalocid A[85].



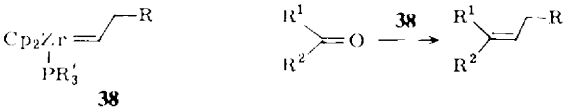
36

The extension of this reaction principle from the transfer of methylene to the transfer of alkylidenes, in general, poses difficulties. By all means, a whole series of α-substituted titanacyclobutanes **37** can be synthesized; however, their cleavage proceeds predominantly with formation of the more highly substituted olefin and the methylene complex **30** [path (a)][81]. The reasons for this are apparently steric and electronic. Thus, the direction of cleavage in the metallacycle can only be reversed if the ring substituents are small and the alkene formed is destabilized [path (b)]. In this way, the substitution of allenes is possible[86].



37

A more general method of alkenylation is based on zirconium complexes of the type **38**. It gives high yields with ketones and lactones, especially when the alkylidene substituent is sterically demanding[87].

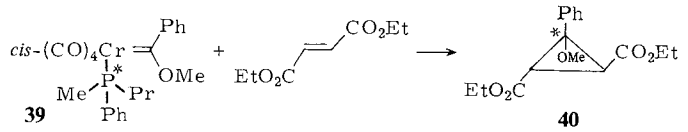


38

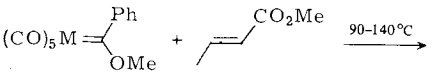
4.3. Cycloaddition Reactions

The most useful reaction of carbenes from a synthetic point of view is their [2+1]-cycloaddition to alkenes[1]. Early studies on carbene complexes of the elements of Group VI already showed that metal-coordinated carbenes could also be used as cyclopropane building blocks[69,88,89]. They can be transferred to electron-deficient as well as electron-rich alkenes. To achieve this, different conditions are necessary; therefore, a single reaction mechanism is unlikely. In no case so far has evidence for the appearance of "free" carbenes been found. Moreover, since the product distribution is metal-dependent, the metal must be involved in the product-determining step. This is also shown by the transfer of chirality from carbene complex **39**, the optical activity of which is due to the phosphane ligand, to the cyclopropane **40**. The cyclopropanation proceeds stereospecifically; the addition of the α-methoxybenzylidene ligand of complexes **1**, **22**, and **23** to unsymmetrically substituted alkenes such as crotonates gives a pair of *syn/anti* stereoisomers **41a/b**, the ratio of which increases along the series M = W, Cr, Mo[89]. The temperature necessary for reaction (≥90°C) would indicate the cleavage of a CO ligand as initial step, followed by coordination of the alkene. A reductive elimination via a metallacyclobutane **42** leads to the cyclopropane. The cyclopropanation of electron-rich olefins such as enol ethers or enamines can be achieved at lower temperatures, but only under CO pres-

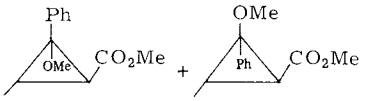
sure[69,90]. Instead of an initial cleavage of CO, a nucleophilic addition of the alkene to the carbene carbon is therefore assumed. As shown by the dependence of the product ratio **43a/b** on the metal, the central metal atom must also be involved in the subsequent course of the reaction.



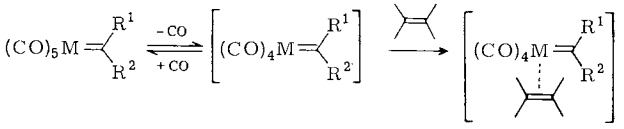
39 **40**



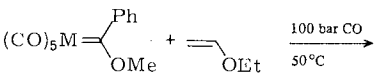
1, M = Cr
22, M = Mo
23, M = W



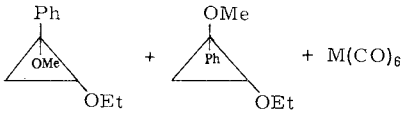
	41a	**41b**
	70	30
	85	15
	68	32



42



1, M = Cr
22, M = Mo
23, M = W



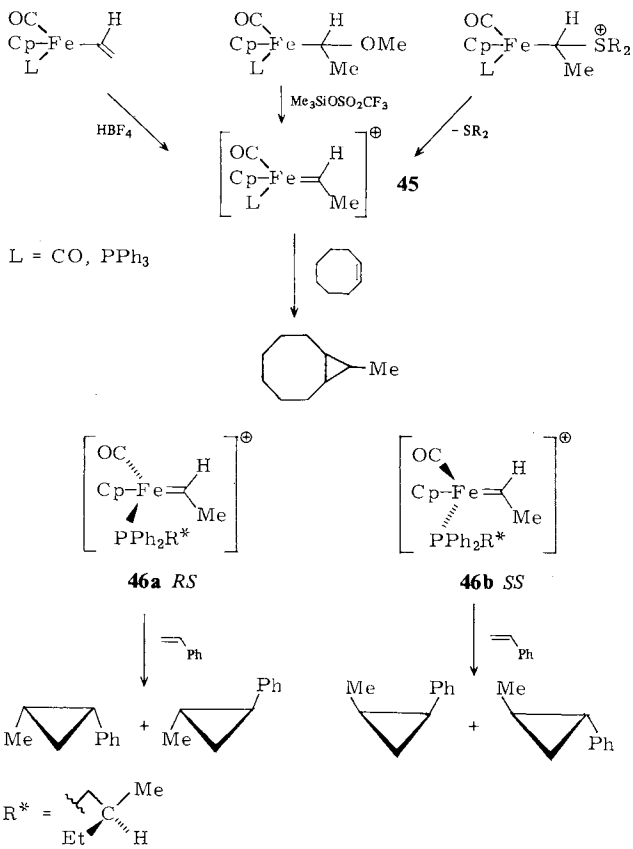
	43a	**43b**
	76	24
	80	20
	64	36

Carbene ligands that are not stabilized by heteroatoms in the α-position can also be transferred to non-activated olefins. Studies on the phenylcarbenetungsten complex **16**, a thermally labile compound which already decomposes at −56 °C with a half-life of 24 min, show that the cyclopropanation is favored by increasing electron density in the alkene[48]. Thus, in competition experiments at −78 °C, isobutene reacts about 320 times faster than propene and about 3500 times faster than ethene. Since the CO exchange in the carbene complex should be markedly slower at this temperature than the carbene transfer to the olefin, a direct attack of the pronouncedly electrophilic phenylcarbene ligand on the less substituted carbon atom of the alkene has been suggested. Surprisingly, with some olefins, such as *cis*-2-butene or 2-methyl-2-butene, the thermodynamically less stable *syn*-cyclopropanes **44a** are preferably formed, a result that has not yet been satisfactorily explained[48,91].

16 **44a** **44b**

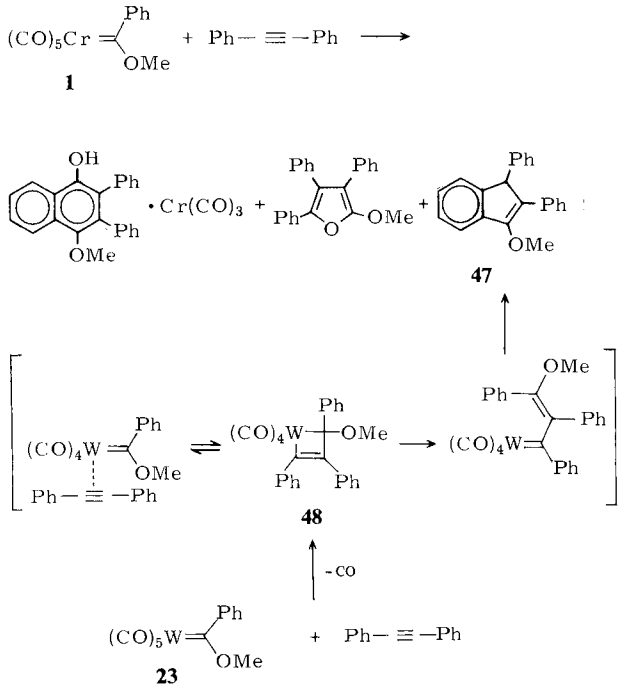
R = H	37	1
R = Me	90	1

In addition to the elements of Group VI, iron also offers an entry to strongly electrophilic carbene ligands. These are obtained from alkenyl, alkoxyalkyl, or dialkylsulfonium-alkyl ligands[23,92,93] and have been transferred to a series of non-functionalized olefins[93-96]. The cyclopropanation takes place, like that for the tungsten complex **16**, with favored formation of the *syn*-configuration[94]. The alkylidene transfer can be made enantioselective by introduction of a chiral phosphane ligand into **45**[97]. The complex cation **46** is obtainable as a pair of diastereomers. Since the diastereomers **46a** and **46b** give cyclopropanes with opposite configurations and, indeed, in practically the same enantiomeric purity, the chirality at the metal is primarily responsible for the optical induction.



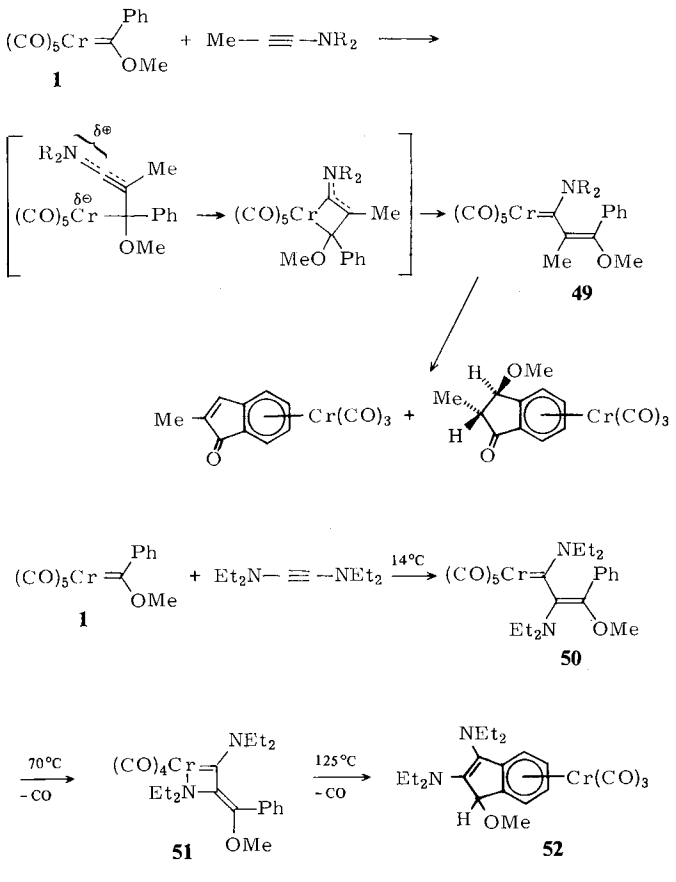
46a *RS* **46b** *SS*

In special cases, phenylcarbene ligands can be annelated by alkynes to give indenes. The first example of this type of reaction was the reaction of the carbene complex **1** with tolane in a poorly coordinating solvent[98]. In addition to other products such as naphthohydroquinone derivatives and furan derivatives, which are formed by cycloaddition of the methoxy(phenyl)carbene ligand, CO ligand, and alkyne, the indene **47** is formed, which is the formal [2+3]-cycloadduct of the alkyne and the carbene ligand. This reaction can be carried out selectively if the chromium

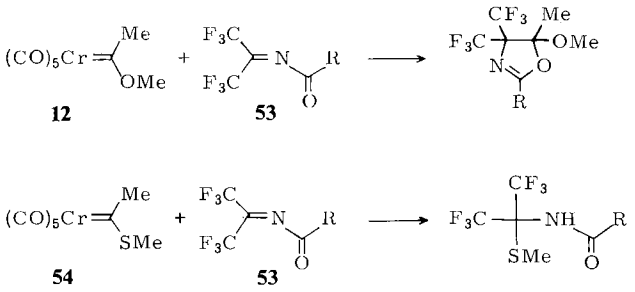


compound **1** is replaced by the analogous tungsten complex **23**[99]. In this case, the stronger metal-carbonyl bond ($\overline{\Delta H}_{W-CO} = 178$ kJ mol^{-1} in contrast to $\overline{\Delta H}_{Cr-CO} = 108$ kJ mol^{-1})[100] prevents insertion of carbon monoxide into the reaction product.

The formation of the indene skeleton could take place via insertion of the alkyne into the metal-carbene bond. Such a reaction sequence has been demonstrated for nucleophilic alkynes. Ynamines and ynyl ethers add to the carbene carbon and are inserted into the metal-carbene bond, possibly via a four-membered metallacycle[45,47,48]. The *E*-styrylcarbene ligand in **49** can be cyclized only in small yield to the indanone and indenone skeleton, probably because of the flexible alkenyl side chain[101]. The course of the reaction can be better controlled if the freedom of motion of the alkenyl side chain is restricted by coordination to the metal. This is clearly demonstrated by the example of an ynediamine, which undergoes 1,3-addition to the phenylcarbene ligand, forming the diaminoindene complex **52** via the isolable intermediates **50** and **51**, the course of the reaction being temperature-controlled[102,103].

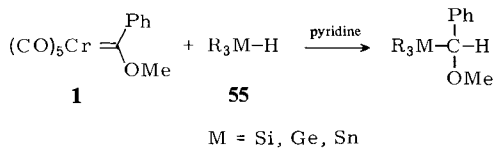


So far, only one example of a [4+1]-cycloaddition is known. *N*-Alkylideneamides **53** react with alkoxy- and aminocarbene ligands, as they do with carbenes or isocyanides, to give dihydrooxazoles[104]. In contrast, the thiocarbene complex **54** undergoes cleavage of the carbene-sulfur bond, and the methylthio group is added to the imine carbon.

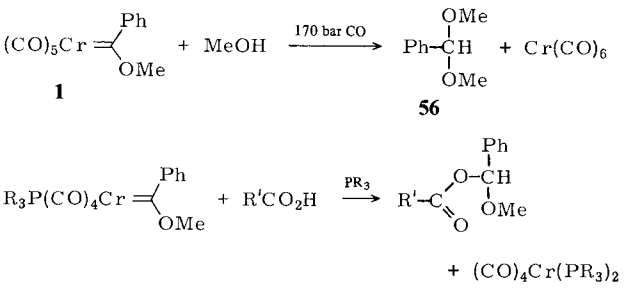


4.4. Insertion Reactions

In addition to cycloadditions to unsaturated compounds, insertion reactions are also a characteristic feature of carbene chemistry which can provide information on the nature of the carbene species. So far, there is no known example for the insertion of a metal-coordinated carbene into a C–H bond. This reaction is regarded as the criterion for the appearance of a "free" carbene[1]. In contrast, carbene ligands insert into the more reactive silicon-, germanium-, and tin-hydrogen bonds[105–107]. The reaction is favored by the presence of a base (e.g. pyridine), which finally replaces the carbene ligand. Kinetic investigations with alkoxy- and aminocarbenechromium complexes and triorganometal hydrides **55** have shown that a dissociative first-order component competes with a predominant, associative contribution that is due to nucleophilic attack of the hydride on the carbene carbon[108,109]. The rate of reaction increases along the series Si < Ge ≪ Sn, which has been interpreted in terms of an increasing tendency towards pentacoordination.



Insertion reactions are also known for oxygen-hydrogen bonds; in the presence of carbon monoxide or phosphanes, the carbonylmetal fragment becomes coordinatively saturated. Thus, the complex **1** reacts with methanol in a CO atmosphere to give the acetal **56**[110], while carboxylic acids are esterified[111].

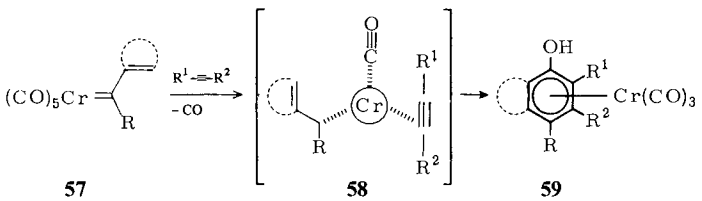


5. Carbonyl-Carbene Transfer Reactions

Carbonylcarbene complexes contain complex-bonded carbon monoxide in addition to the carbene ligand. The wide use of carbonylmetal compounds in carbonylation reactions[112,113] would suggest that the carbonyl ligand in the carbene complex might also be used for syntheses. The bifunctional behavior of this class of compounds is manifested in their reactions with alkynes and Schiff bases.

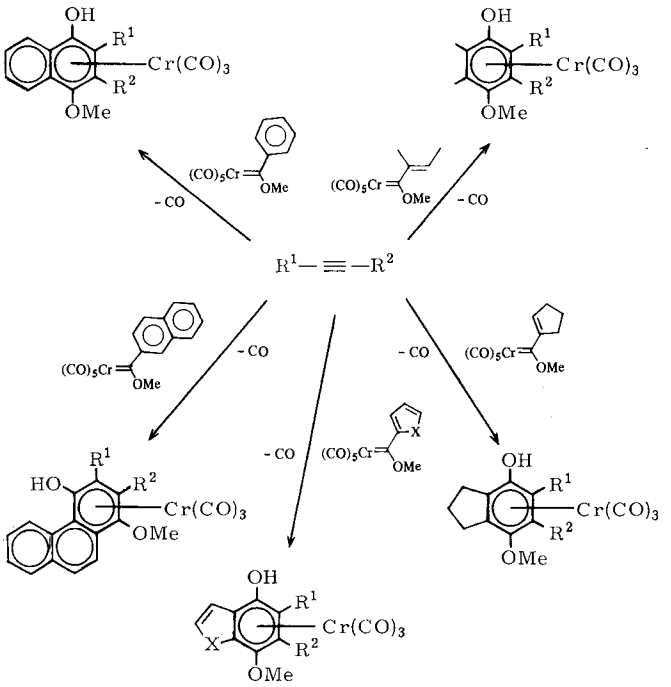
5.1. Cocyclization with Alkynes

Bond formation of carbenes *and* carbon monoxide with alkynes can be carried out at a chromium center[114]. The prerequisite is that the three components have to be directly coordinated to the metal. If pentacarbonylcarbene complexes and alkynes are used, the free coordination site required can be created by a thermally or photochemically induced cleavage of a CO ligand. The CO cleavage depends on the donor-acceptor ability of the carbene ligand and parallels the electrophilicity of the carbene carbon atom, e.g., along the series $:C(NR_2)Ph < :C(OR)Ph < :CPh_2$. In the octahedrally arranged pentacarbonylcarbene complexes, four *cis*-CO ligands and one *trans*-CO ligand can be differentiated. In accordance with the relative donor-acceptor properties of carbene and carbonyl ligands, the elimination of a *cis*-CO ligand is expected to be favored; this is confirmed by CO-exchange studies[115]. Starting with complex **57**, which contains an unsaturated carbene ligand, the addition of the alkyne to the free coordination site leads to a facial alkyne-carbene-carbonyl complex **58**. This reactive intermediate has not yet been isolated. It undergoes rather a clean cycloaddition reaction to give an aromatic six-membered ring which is π-bonded to the metal (Scheme 4)[116].



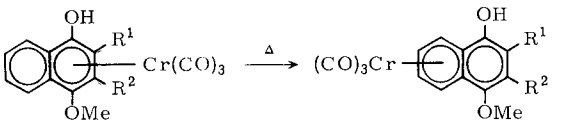
Scheme 4. Cycloaddition of alkyne, carbene, and carbonyl ligands bonded to a chromium center. Ⓒr = Cr(CO)$_3$.

The alkyne is incorporated into the 2,3-position of the hydroquinone derivative **59**. The C-4—C-6 ring positions come from the carbene ligand, whereas C-1 is contributed by the carbonyl ligand. The cycloaddition takes place in donor solvents (e.g., ethers) under mild conditions (40—60°C); the yields are usually 60—90%. The formation of the arene complex **59** is not limited to vinyl-[117] and phenylcarbene substituents[114,118,119]. Carbocycles, heterocycles, and polycyclic arene ligands[120] can also serve as carbene ligands for the synthesis of complexes with benzoannelated arenes (Scheme 5). The metal is always bonded to

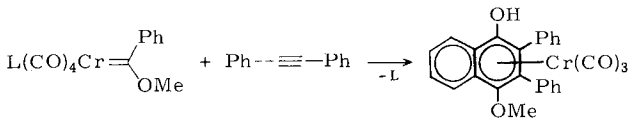


Scheme 5. Benzoannelation of carbene ligands.

the newly formed aromatic ring under conditions of kinetic control. However, in the naphthalene complexes **60** metal migration to give the thermodynamically more stable 4a-8a-η^6-compounds **61** occurs if longer reaction times and higher reaction temperatures are used.



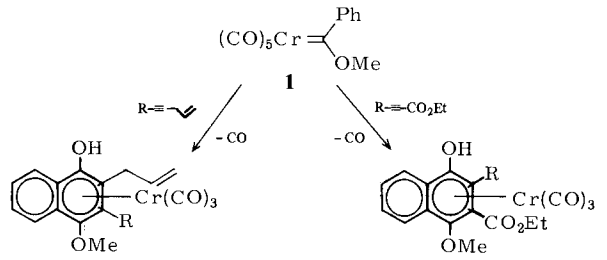
The formation of a free coordination site in the carbonylcarbene complexes can be influenced by other ligands. It is facilitated by good acceptor ligands, as shown by the series of carbene complexes **1**, **62a**, and **62b**. Thus, the



1, L = CO	3 h/45 °C	62%
62a, L = P(*p*-FC$_6$H$_4$)$_3$	2.5 h/60 °C	61%
62b, L = P(*n*Bu)$_3$	2.5 h/90 °C	11%

yield for the reaction with tolane decreases to ca. 1/6 when carbon monoxide or tris(*p*-fluorophenyl)phosphane is replaced by the weaker acceptor tributylphosphane[120].

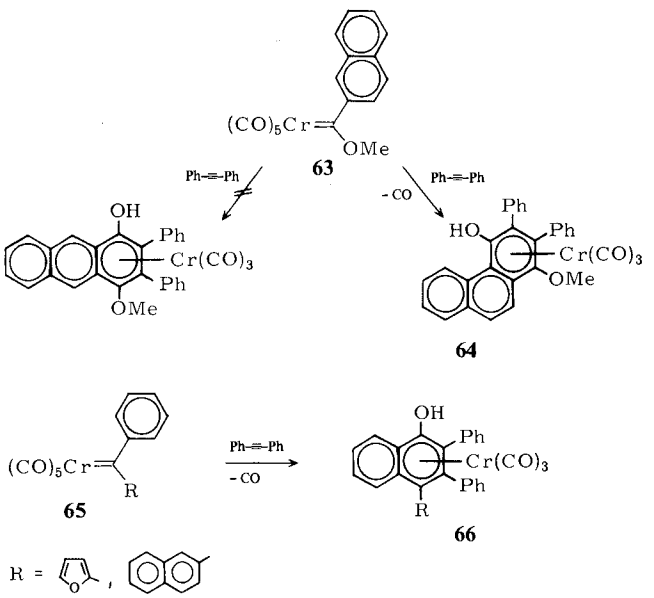
In addition to aliphatic and aromatic alkynes, functionalized derivatives can also be used as the alkyne component. Besides alkynoates[118,121], non-conjugated enynes[122] are suitable since the bond formation between the carbene ligand and the C≡C bond in the cycloaddition proceeds appreciably faster than the cyclopropanation. For this reason, the cycloaddition is also interesting for the synthesis of more complex structures.



An important criterion for the value of a cycloaddition is its regioselectivity. In the present case, the regioselectivity relates to

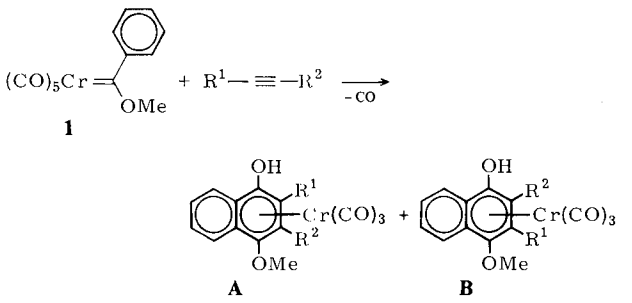
a) a carbene substituent which offers two possibilities for annelation[120],
b) a competing annelation, such as expected for diarylcarbene ligands[120], and
c) the incorporation of unsymmetrical alkynes into the aromatic ring[117,119,120,123].

The regioselective annelation of a carbene substituent is exemplified by the 2-naphthylcarbene complex **63**. The new ring can, a priori, be joined to either the 1-position or the 3-position. Exclusively the phenanthrene complex **64** is isolated from the reaction with tolane. Only when the 1-position is blocked by substitution is the anthracene system obtained[124]. Similarly, in the diarylcarbene complexes



65, which bear a furyl or a naphthyl substituent in the carbene ligand in addition to a phenyl ring, annelation of the phenyl ring is preferred, so that naphthol complexes **66** are formed.

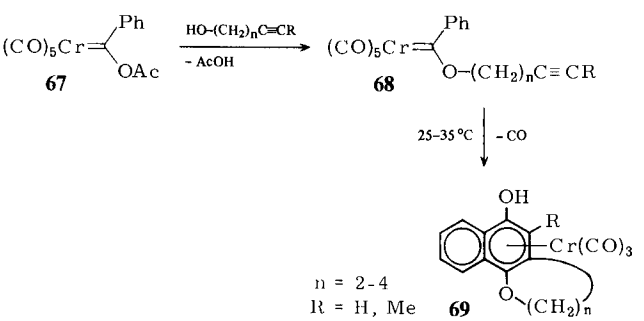
The regioselectivity of the alkyne incorporation depends strongly on the alkyne. In the reaction with methoxy(phenyl)carbene complexes such as **1**, it increases in going from diaryl- to dialkylalkynes and to terminal alkynes (Scheme 6)[119,123]. This trend also holds for vinylcarbene complexes[117]. Tolane derivatives that are partly selectively substituted in the *p*-position give both possible regioisomers **A** and **B** in approximately equal amounts. With 2-al-



R^1	Ph	*p*-MeC_6H_4	Et	Phytyl	*t*Bu	Ph	Pr	Octyl
R^2	*p*-$CF_3C_6H_4$	*p*-$CF_3C_6H_4$	Me	Me	Me	Me	H	H
A/B	54/46	56/44	69/31	63/37	92/8	>97/<3	>97/<3	>97/<3

Scheme 6. Regioselective incorporation of alkyne in the reaction with **1** to give isomers **A** (~**60**) and **B**.

kynes, the isomeric ratio increases to about 2:1. Isomer **A**, in which the longer side chain is adjacent to the hydroxy group, always predominates. The example of methylphytylacetylene shows that the length of the side chain has no effect. In contrast, the regioselectivity is improved by α-substitution in the alkyne (e.g. in 4,4-dimethyl-2-pentyne). Another point to consider is the incorporation of the alkyne component into the carbene ligand[125]. The cycloaddition can thereby take place intramolecularly, which consequently reduces the conformational freedom. The required alkynyloxycarbene complex **68** can be obtained by nucleophilic addition of the alkynol to the acetoxycarbene compound **67**, which can be regarded as an organometallic analog of an anhydride. The cycloaddition of **68** proceeds smoothly with internal triple bonds (R = Me), providing a good extension of the intermolecular variant of the reaction. Carbene substituents with terminal alkyne functions (R = H), however, give only moderate yields of the tricyclic compounds **69**. On the other hand, terminal

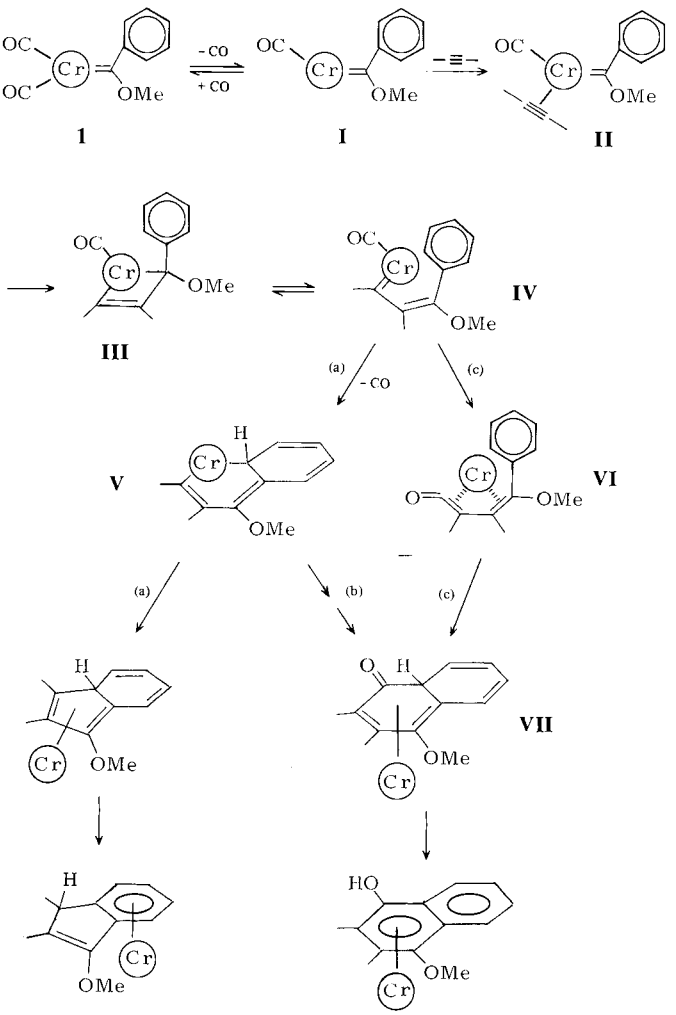


alkynes, as well as the arylalkylacetylene 1-phenyl-1-propyne, are incorporated regiospecifically even in the intermolecular reaction within the detection limits of NMR spectroscopy (±3%). Only isomer **A**, in which the sterically more demanding alkyne substituent is present in the more accessible 2-position, can be observed. This finding indicates that the regioselectivity of alkyne incorporation is mainly controlled by steric factors, which favor bond formation between the carbene carbon and the spatially less-shielded alkyne carbon atom.

5.2. Vinylketenes as Intermediates

Initial studies on the reaction mechanism had shown that the cycloaddition is suppressed by the presence of carbon monoxide[118]. This finding pointed to cleavage of CO in the first step, which was later confirmed by a more thorough kinetic study[126]. Accordingly, the kinetic parameters found for the reaction of the methoxy(phenyl)carbene complex **1** with tolane, a relatively high activation enthalpy ($\Delta H^{+} = 108 \pm 2$ kJ mol^{-1}) and a positive activation entropy ($\Delta S^{+} = 26 \pm 6$ J mol^{-1} K^{-1}), are characteristic of substitution reactions in carbonyl carbene complexes that take place by a dissociative mechanism[127]. The elimination of carbon monoxide gives a coordinatively unsaturated tetracarbonyl carbene complex, for which the alkyne and the cleaved CO ligand compete (Scheme 7). The re-addition of the carbon monoxide takes place faster than complex formation with the alkyne. The rate of alkyne coordination increases with increasing electron density in the alkyne function. Thus, in CO-saturated dibutyl ether, the coordination of 1-phenyl-1-propyne takes place about 5 times faster than that of the more electron-deficient tolane; it is, however, still 40 times slower than the addition of carbon monoxide. Since the CO substitution takes place preferably in the position *cis* to the carbene ligand[115,128], an intermediate **II** is formed in which the metal fixes the three different ligands in a facial configuration, i.e. on an octahedral surface. In comparison with the first two reaction steps, the subsequent steps proceed so fast that the kinetics of the reaction provides no further information about them. Nonetheless, it is plausible to assume bond formation between the alkyne and carbene ligands in the next step to give chromacyclobutene **III**, the ring opening of which results in a coordinatively unsaturated alkenylcarbene complex **IV**. From here, several reaction pathways are conceivable[7,116]:

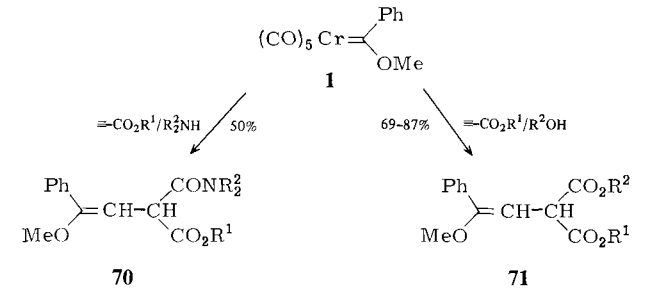
a) The oxidative addition of the phenylcarbene substituent to the metal gives a chromacyclohexadiene **V**, which via σ-π rearrangement, re-aromatization, and metal migration results in an indene complex.
b) The chromacyclohexadiene **V** could undergo a CO insertion into the metal-carbon bond and give, via σ-π rearrangement, a chromium-coordinated cyclohexadienone **VII**, which then isomerizes to the naphthol complex.
c) Alternatively, the formation of the naphthol skeleton can take place via carbonylation of the alkenylcarbene carbon in **IV** to give the vinylketene complex **VI**, which undergoes an electrocyclic 1,6 ring-closure involving the phenyl substituent and gives the naphthol complex via cyclohexadienone **VII**.



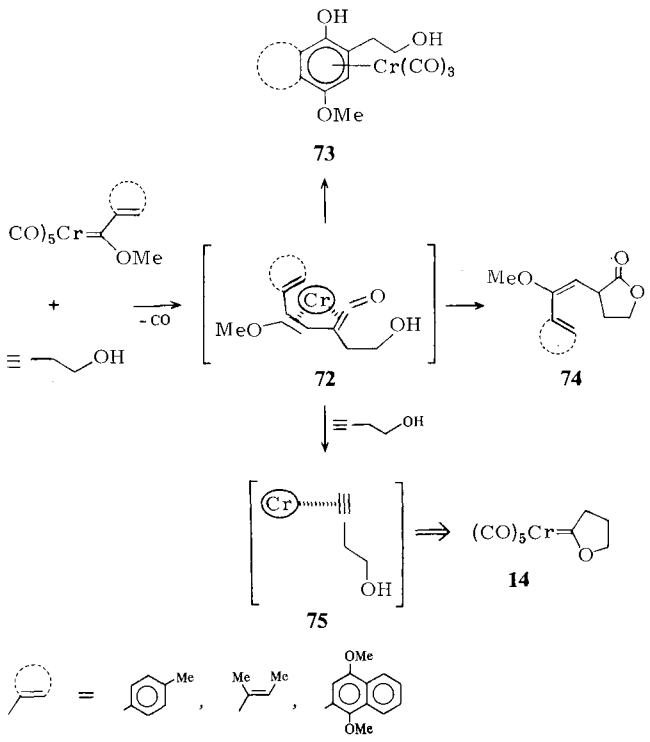
Scheme 7. Discussion of the reaction mechanism. (a)—(c), see text. Cr ≡ Cr(CO)$_3$.

According to Scheme 7, the chromacyclobutene **III** and the vinylketene **VI** are key intermediates. Thus, the observed regioselectivity of the alkyne incorporation and of the annelation of diarylcarbene ligands can be traced back to a selective formation of the metallacycle from alkyne and carbene ligands as well as to a selective ring opening. The occurrence of coordinatively unsaturated intermediates demonstrates that a donor solvent is necessary for a smooth reaction.

Of the suggested reaction pathways, the vinylketene route (c) is supported by a series of experimental results. Thus, bond formation between carbene and carbonyl ligands in iron[129] and manganese compounds[130] is well known and has recently also been shown for pentacarbonyl(diphenylcarbene) complexes of chromium and tungsten[131]. Because of its diene-like coordination to the metal, the vinylketene ligand in **VI** should exist in the *s-cis*-conformation. Hence, a 1,4 ring closure to give cyclobutenone is expected to take place if the phenyl ring is replaced by a carbene substituent that cannot undergo annelation. This is confirmed by the reaction of methoxy(methyl)carbene complex **12** with tolane[132].



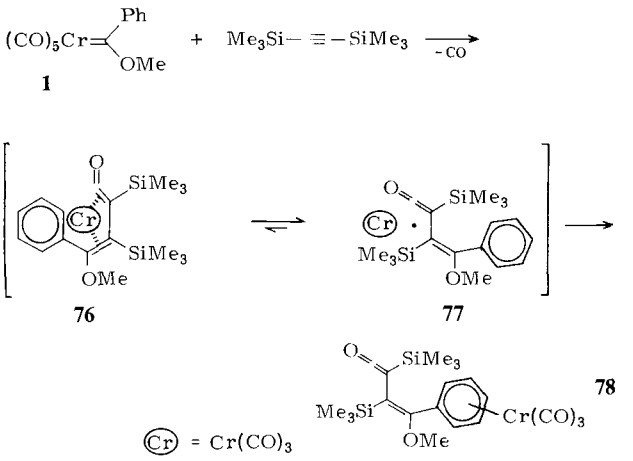
Bond formation between alkyne, carbene, and carbonyl ligands to give vinylketenes is further supported by trapping experiments. Thus, the carbene complex **1** reacts with propiolate in the presence of amines or alcohols to give the α,β-unsaturated 1,3-dicarbonyl compounds **70** and **71**, respectively[133]. The relative rates of such trapping reactions and of the cycloaddition should be determinable if alkyne and alcohol functions are combined together in the form of alkynols: A vinylketene intermediate **72** will then be formed, which can undergo annelation of the carbene substituent to give the arene skeleton **73** as well as addition of the alcohol to the ketene group to give the lactone **74**. This competition can be controlled by the choice of carbene ligands (Scheme 8)[134]. Both ring-closure reactions take place at comparable rates when *p*-tolylcarbene complexes are allowed to react with 3-butyn-1-ol. However, with the *E*-2-butenylcarbene complex, only the hydroquinone **73** is isolated. In contrast, the annelation of the naphthylvinylketene **72** proceeds so slowly that only the lactone **74** is obtained. On ring closure of the vinylketene **72** to give lactone **74**, the carbonylchromium fragment is set free. It adds to excess alkynol to give **75** and can be isolated as the



Scheme 8. Annelation (**73**) *versus* lactone formation (**74**).

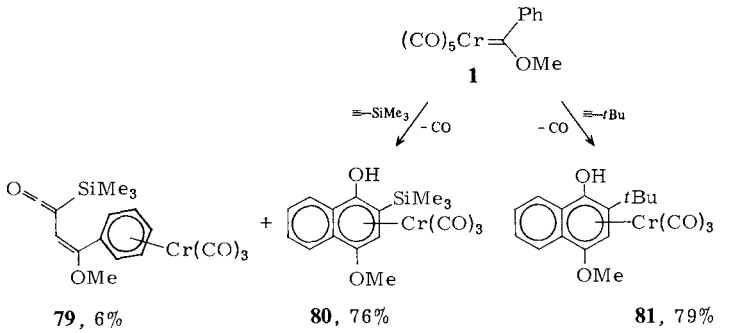
tetrahydro-2-furylidene complex **14**. This reaction course is confirmed by reaction of the alkynol with solvent-stabilized carbonylmetal fragments such as $(CO)_5Cr \cdot OEt_2$[135].

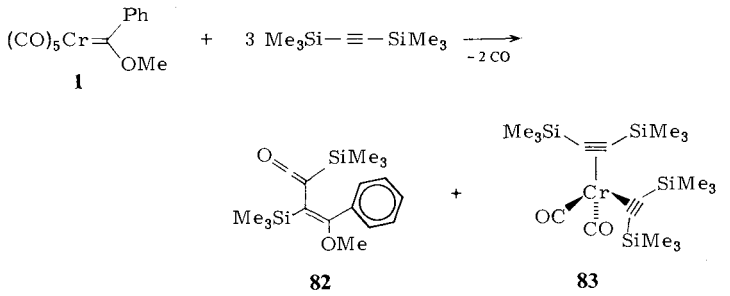
Besides trapping reactions, the isolation of stable compounds also supports the appearance of vinylketenes. These experiments are based on the argument that the *s-cis* conformation **76** of the vinylketene ligand will be forced by sterically demanding substituents R of the central C–C bond to assume an *s-trans* conformation **77** and thereby be prevented from undergoing a subsequent ring closure. The central C–C bond is derived from the alkyne; therefore, bis(trimethylsilyl)acetylene was chosen as the alkyne component. Arylvinylketenes that are coordinated by the aryl group to the metal are thus obtained from a series of arylcarbene complexes[136, 137]. They are sufficiently stabilized by the silyl substitution to allow investigation of their stereochemistry and bonding by X-ray analysis. It was shown for the phenyl compound **78** that the ketene and olefin moieties are separated by a pure CC single bond (1.51 Å) and form a dihedral angle of 77° along this axis[138]. Any



electronic interaction is thus obviated. The isolation of the vinylketene can be traced back to the steric and electronic properties of the trimethylsilyl group. Thus, in the case of trimethylsilylacetylene, the formation of the vinylketene **79** can hardly compete any longer with the cycloaddition to give the naphthohydroquinone skeleton **80**[137], and, if the even bulkier *tert*-butyl group is substituted for the trimethylsilyl function, only the hydroquinone **81** is obtained[119]. The diene-like coordinated vinylketene in **76** is displaced by excess bis(trimethylsilyl)acetylene. In this way, metal-free vinylketenes **82** and isolable bis(alkyne)dicarbonylchromium **83** are obtained[139].

Spectroscopic studies indicate that the vinylketene system is practically unaffected by the complexation of the aryl ring. Its reactivity is markedly lower in comparison with silyl-free vinylketenes[140], which usually cannot be isolated. The addition of nucleophiles, such as amines and alcohols, to give carboxylic derivatives is relatively slow, and, even with typical ketenophiles such as enol ethers and enamines, no cycloaddition takes place[141]. With the more strongly nucleophilic ynamines, addition to the C=C bond competes with addition to the C=O bond (Scheme 9)[142, 143]. The reaction products, cyclohexadienone **86** and

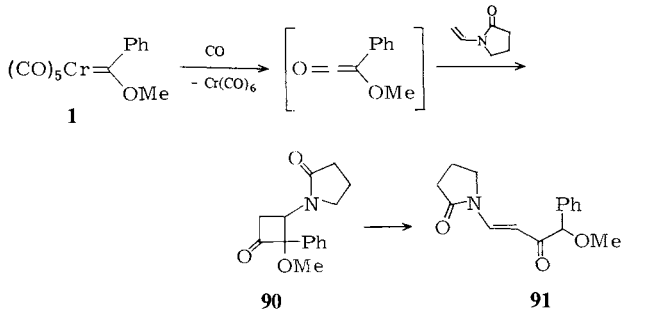




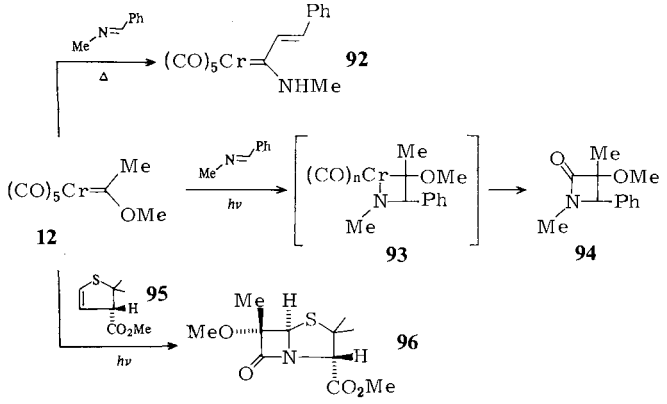
endo-R-bicyclo[3.1.0]hexenone **87**, can be traced back to the common cyclobutenone and dienylketene intermediates **84** and **85**, respectively; the formation of allenamide **89** is explained by an intermediate dihydrooxete **88**.

5.3. Cocyclization with Enamines and Schiff Bases

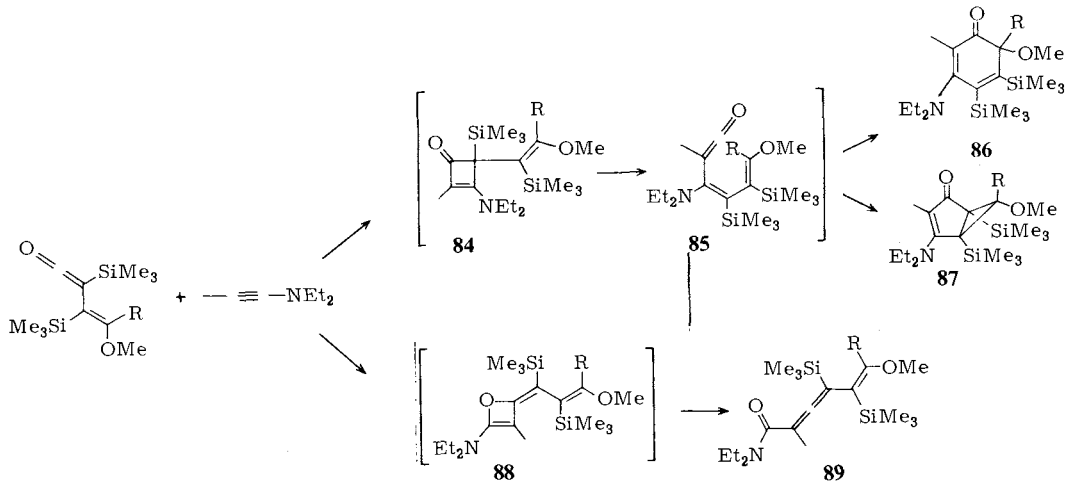
Besides alkynes, several double bond systems are known that undergo bond formation with carbene and carbonyl ligands. On heating with *N*-vinylpyrrolidone, the methoxy(phenyl)carbene ligand in **1** is alkenylated to give α-methoxystyrene[72], whereas bond formation between the alkene, carbene, and carbonyl components takes place under additional CO pressure. The enamino ketone **91** is obtained, albeit in modest yield, via ring opening of the pyrrolidonecyclobutanone **90**, a complex that can be isolated by using 2,2-disubstituted vinylpyrrolidones[144]. Methoxyphenylketene, formed by carbene-carbon monoxide coupling, is assumed to be an intermediate.



The reaction conditions prove to be a critical factor in the reaction of the methoxy(methyl)carbene complex **12** with Schiff bases[145-147]. Under thermal conditions, the acidity of the methylcarbene substituent, which is functionalized to give the alkenyl(amino)carbene system **92**, dominates. On the other hand, cycloaddition to give β-lactam **94** takes place upon UV irradiation. The formation of the four-membered ring appears to proceed stereospecifically; according to NMR spectroscopic analysis, only *one* diastereomer is formed. The (*S*)-dihydrothiazole ester **95** is converted into the diastereomerically pure penam system **96** according to the same criterion. Acyclic Schiff bases, however, effect a smaller asymmetric induction. A



Scheme 10. Photo-induced cycloaddition of carbonylcarbene complexes and Schiff bases.



Scheme 9. Competing pathways for the addition of ynamines to bis(silyl)vinylketenes.

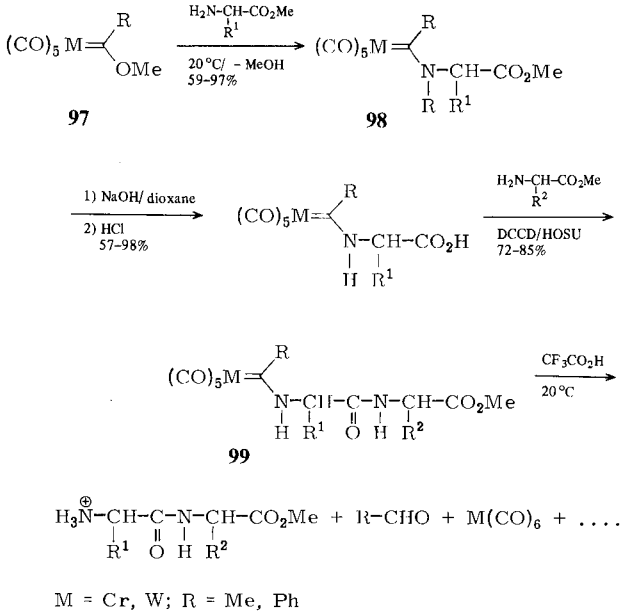
reaction mechanism cannot involve the nucleophilic attack of the imine nitrogen on the carbene carbon since this step would lead to a 3-azetidinone ring instead of a β-lactam (2-azetidinone) structure. Instead, reversal of the polarity of the metal-carbene bond in the photo-excited state is proposed. This should react with the Schiff base to give the β-lactam **94** via the chromacycle **93** (Scheme 10).

6. Synthesis of Natural Products

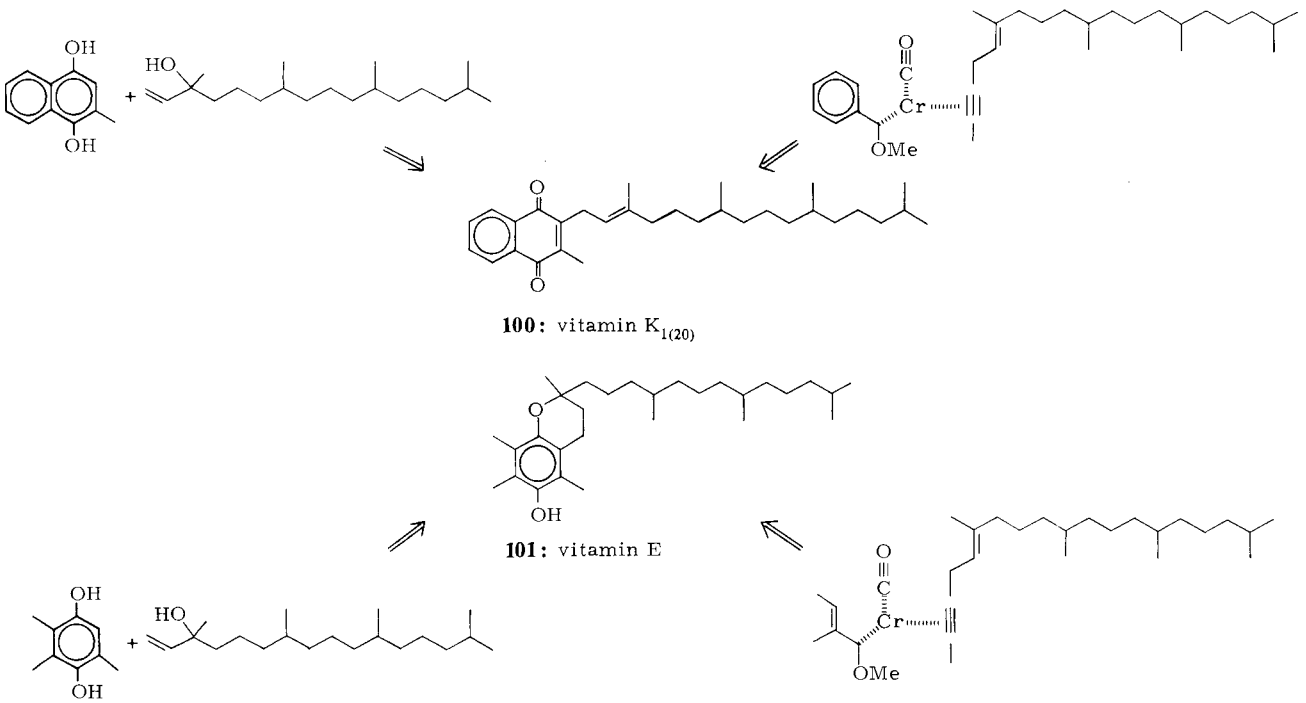
The simple preparation of alkoxycarbenecarbonyl complexes, their easy manipulation, and the possibility of functionalizing them make these reagents of interest in natural product synthesis. The examples so far known are based on the electrophilicity of the carbene carbon, on the one hand, and on the cycloaddition of alkyne, carbene, and carbonyl ligands to form the hydroquinone skeleton, on the other.

6.1. Peptide Synthesis

The smooth aminolysis of alkoxycarbene complexes was the impetus for the use of the "metalcarbenyl" function as a protecting group in the synthesis of peptides. Similarly to primary or secondary amines, amino acid esters react with pentacarbonyl(methoxycarbene) complexes of chromium and tungsten **97** to give the aminocarbene complexes **98**[148,149]. Because of the nucleophilicity of carboxylate ions, the amino acids have to be protected by esterification. However, no further protection is necessary for other groups, such as hydroxy groups or heterocyclic nitrogen groups in serine and histidine esters. The aminolysis is not limited to α-amino substituents; both the α- and the ε-amino groups in lysine react because of their similar nucleophilicity, so that lysine derivatives protected on N^{α} and N^{ε} by carbene complexes are formed. In order to form the peptide bond, the conventional method is used, namely saponification of the ester followed by coupling of the second amino acid ester component in the presence of dicyclohexylcarbodiimide/*N*-hydroxysuccinimide (DCCD/HOSU method)[150]. The cleavage of the amino protecting group from **99** is accomplished under mild conditions at 20°C with trifluoroacetic acid (Scheme 11). This step proceeds most cleanly with phenylcarbenechromium complexes. The utility of the method has been demonstrated by the stepwise synthesis of the tetrapeptide Gly-Gly-Pro-Gly-OMe, which is present as sequence 14—17 in the human proinsulin C-peptide[149].



Scheme 11. Metalcarbenyl functions as *N*-terminal protecting groups in peptide synthesis. The last step can also be carried out with acetic acid at 80°C (74—83% yield).

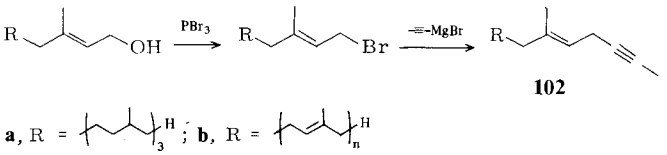


Scheme 12. Synthetic strategies for the synthesis of vitamins K and E.

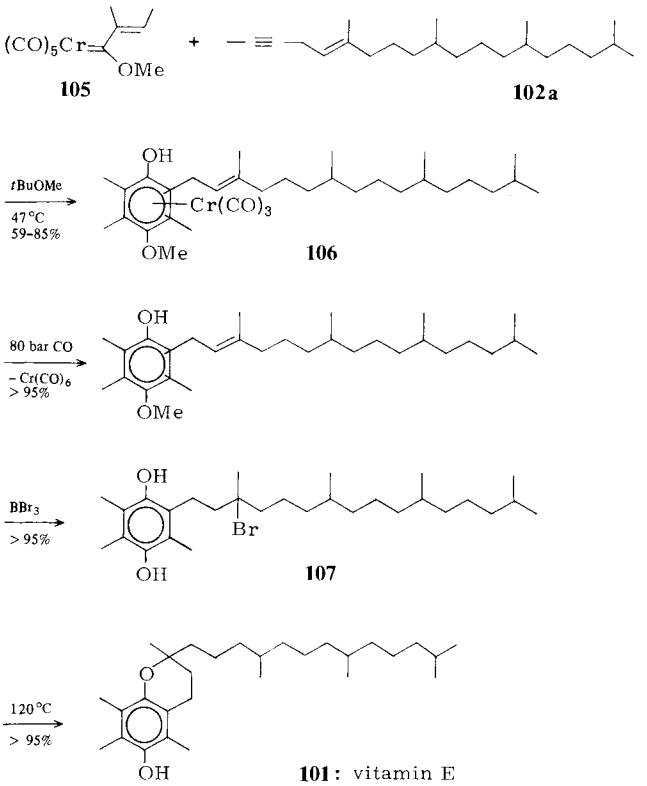
6.2. Synthesis of Vitamins K and E

The conventional synthesis of vitamins K **100** and E **101** is based on the condensation of isoprenoid alcohols with hydroquinones[151]. In contrast, a carbene-complex route to these compounds aims at the formation of the hydroquinone ring within the coordination sphere of chromium(0) (Scheme 12)[116].

The synthesis of vitamins of the K series starts with the methoxy(phenyl)carbene complex **1** and the enynes **102**, which are easily obtainable from the commercially available isoprenoid alcohols via the bromides using a Grignard propynylation[152, 153]. The cycloaddition in a low-boiling



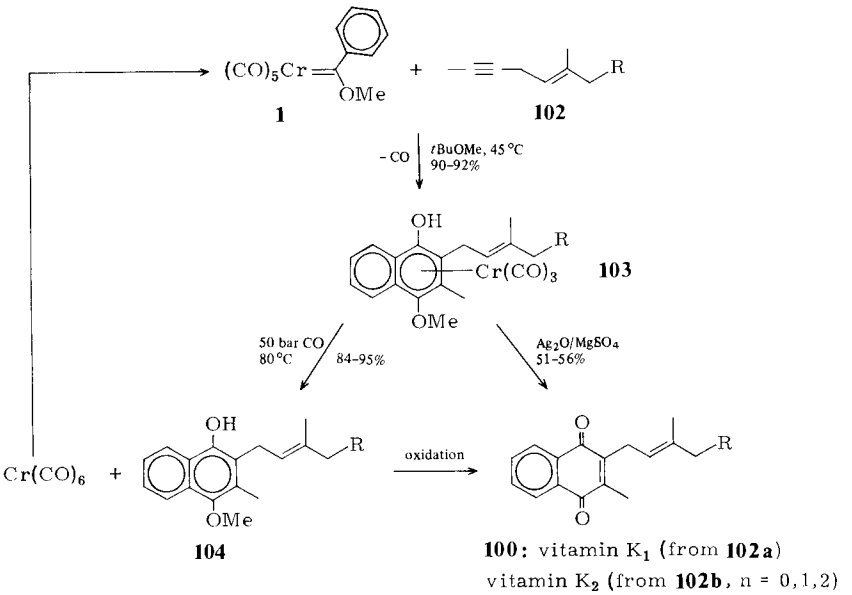
ether gives a 2:1 mixture of regioisomers of the dihydrovitamin K monoether complex **103** in 90% yield. The isomers can be separated by column chromatography using silica gel; however, this is not necessary for the subsequent course of the synthesis. Cleavage of the metal-arene bond is basically possible in two different ways: by oxidation or by ligand exchange. Oxidation with silver(I) oxide gives vitamin K directly. However, the yield is only about 55% and the chromium is converted into valueless chromium(III). These disadvantages can be avoided by a ligand substitution under CO pressure. The $Cr(CO)_3$ fragment is released practically quantitatively as hexacarbonylchromium, which serves as starting compound for the preparation of the carbene complex and can therefore be reused in a cyclic process. The oxidation of the dihydro-vitamin K intermediate **104** is then carried out using the conventional procedure (Scheme 13). In contrast to the condensation route, in which partial isomerization of the allylic double bond cannot be avoided because of the acidic medium required, the cycloaddition takes place with retention of con-



Scheme 14. Carbene-complex route to vitamin E.

figuration. This is important insofar as only the *E* isomer of vitamin $K_{1(20)}$, the most important K vitamin, is biologically active[154].

Vitamin E can also be synthesized according to a similar reaction sequence. A suitable starting material is the *E*-2-butenylcarbene complex **105**, which is obtained stereospecifically from *E*-2-bromo-2-butene[155]. The cycloaddition with the C_{23}-enyne **102a** gives the tricarbonylchromium complex **106** as a 70:30 mixture of the two regioisomers, from which the metal is cleaved as $Cr(CO)_6$ under CO pressure. In order to use both regioisomers for a ring clo-

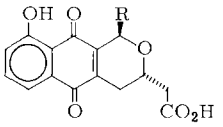


Scheme 13. Carbene-complexes route to the vitamins of the K series.

sure to give the chromane skeleton, cleavage of the ether is necessary. This is best achieved with boron tribromide, the allylic double bond being hydrobrominated simultaneously. The cyclization of the bromine derivative **107** to give vitamin E **101** can be carried out in the presence of Lewis acids according to the method of *Karrer* et al.[156] or, in practically quantitative yield, by heating to 120°C (Scheme 14)[157].

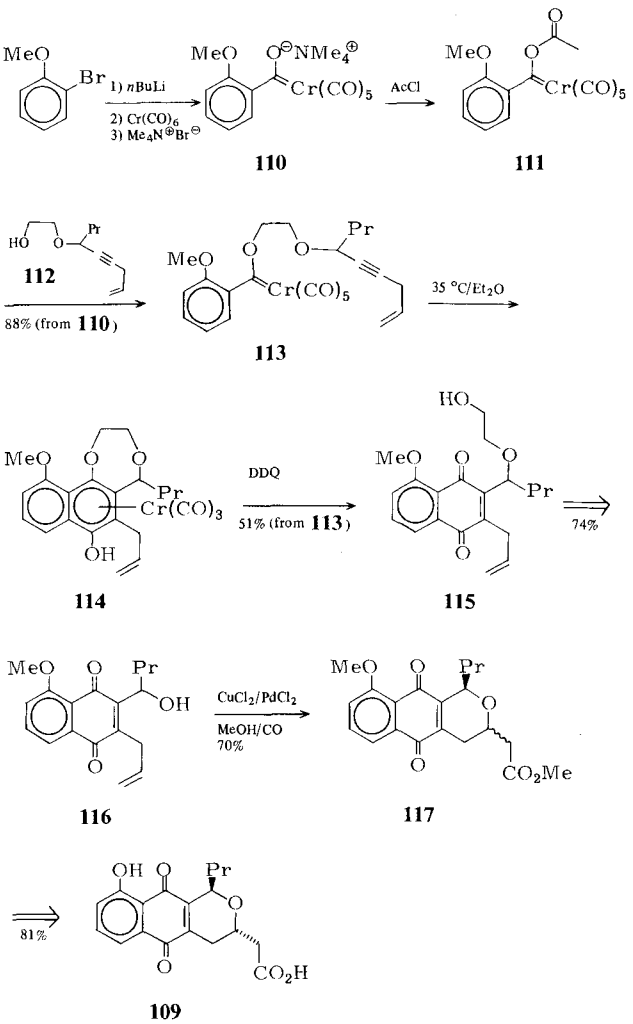
6.3. Synthesis of Antibiotics

The naphthoquinone skeleton appears as a part of the structure of a series of antibiotics. For example, it is combined with a dihydropyran ring in nanaomycin A **108** and deoxyfrenolicin **109**. A carbene-complex route to this

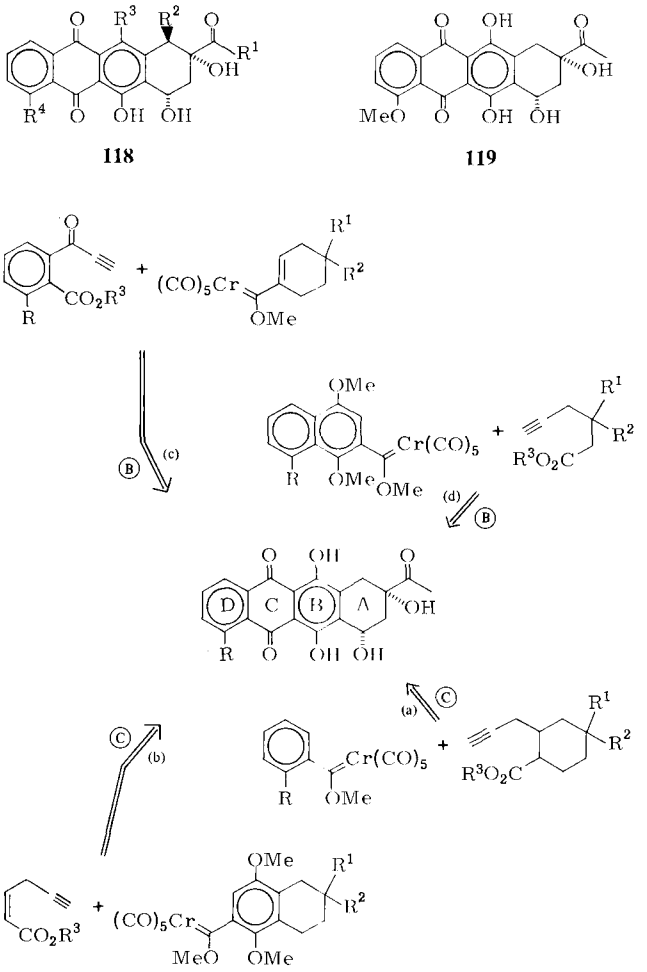


108, R = Me
109, R = Pr

compound is based on two key reactions: the formation of the quinone ring by a cycloaddition reaction, and the intramolecular alkoxy carbonylation of a hydroxy alkene to give the oxygen-containing heterocycle[158].



Scheme 15. Synthesis of deoxyfrenolicin **109** by intramolecular carbene addition and alkoxycarbonylation.



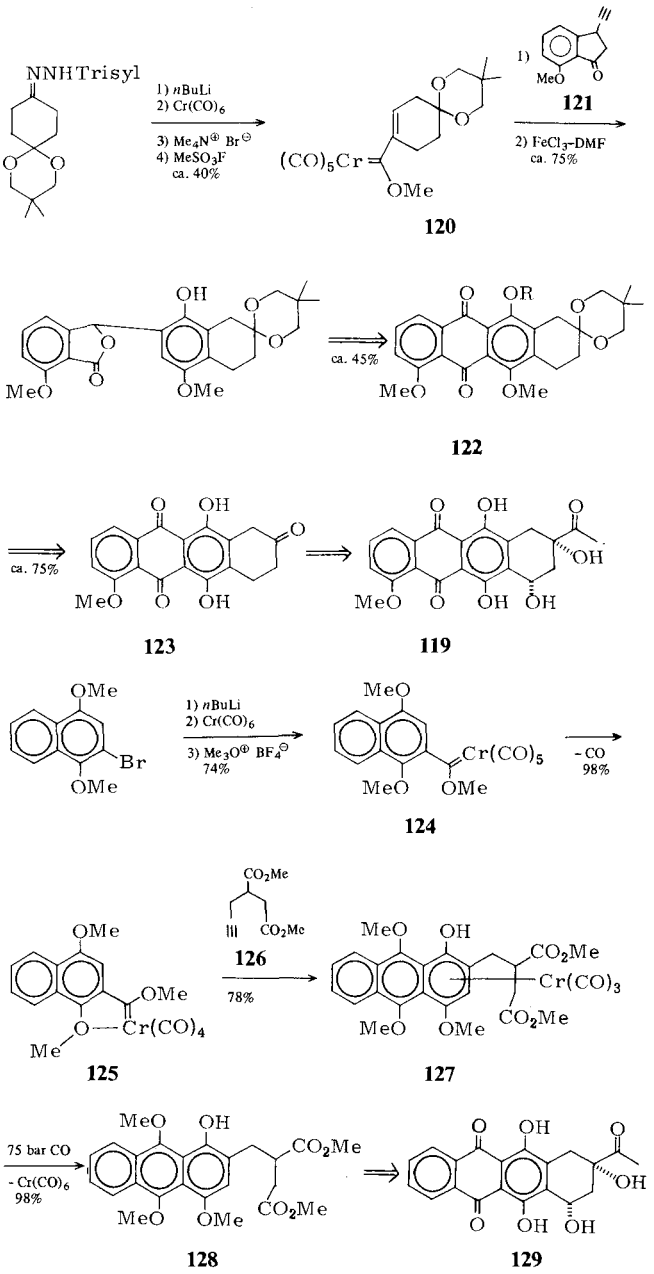
Scheme 16. Carbene-complex strategies to the daunomycinone skeleton. (a)—(d), see text.

The acyl chromate, which is storable and easy to handle as the tetramethylammonium salt **110**, is obtained by addition of 2-lithioanisole to hexacarbonylchromium. Its acetylation gives the acetoxycarbene complex **111**, which, since it is an "anhydride analog", is cleaved by the hydroxyenyne **112**. The alkynyloxycarbene compound **113** undergoes an intramolecular cycloaddition to give the hydroquinone complex **114**. It is oxidized with 2,3-dichloro-5,6-dicyanoquinone (DDQ) to give directly the quinone **115**, which is finally isolated in 51% yield. After cleavage of the alcohol protecting group, a hydroxyalkene structure is present in **116** which enables a palladium-catalyzed alkoxycarbonylation to give the dihydropyran. Thereby, **117** is formed as a *cis/trans* mixture (25:75). However, during the subsequent demethylation with boron tribromide, a complete isomerization to the natural *trans*-configuration takes place (Scheme 15).

Anthracyclinones offer an ideal target for the carbene-complex route. They are the aglycones of the anthracyclines, which at present are being intensively studied and which have proven to be effective anti-tumor agents[159]. They have a basic tetracyclic skeleton **118**, which always has a quinoid ring C and, in many cases, including the most important representative of this series, daunomycinone **119**, a hydroquinone system B. The synthesis of daunomycinone can follow four independent routes, each

starting with a carbene complex and an alkyne (Scheme 16). Thus, the quinone ring C might be formed either from the anisylcarbene complex and an alkyne ester containing ring A [route (a)] or from the bicyclic carbene complex and a 1,4-enyne ester [route (b)]. Alternatively, a ring closure to give the hydroquinone ring B may be considered. The basic principle of route (c) is realized in the cycloaddition of the cyclohexenylcarbene complex **120** and the ethynyl lactone **121**[160]. The C and D ring components can, however, be introduced via the carbene ligand. Following annelation of the carbene ligand with the alkyne ester to give the hydroquinone, the A ring must be closed in the next step [route (d)][161].

The cyclohexenylcarbene complex **120** was prepared from the hydrazone[160]. The cycloaddition with an acylacetylene according to route (c) (Scheme 16), however, proceeded in only small yield; it proved more advantageous, therefore, to use the lactone **121** as alkyne component. **121** is readily obtainable from 2-methoxybenzamide and propargyl aldehyde. After oxidative cleavage of the $Cr(CO)_3$ fragment, ring C is closed and oxidized to the quinone, using a protecting group for the hydroxy function. A dealkylation in the hydroquinone ring finally affords the triketone **123**, the A ring of which can be further functionalized to give daunomycinone **119**[162] (Scheme 17).



Scheme 17. Carbene complex route to daunomycinone **119** and derivatives such as **129**. DMF = dimethylformamide.

An alternative route consists of the annelation of the CD-ring building block, which is introduced by the carbene ligand, prepared from 2-bromo-1,4-dimethoxynaphthalene[124]. Arylcarbene complexes with alkoxy functions in the *ortho* position, such as **124**, readily undergo displacement of a *cis* CO ligand by the arylalkoxy group[163]. A tetracarbonyl complex **125** containing a chelating carbene ligand is thereby formed quantitatively. Such compounds are practically air-stable and therefore very useful as storable starting materials. As shown by the X-ray structure analysis of the analogous methoxy(*o*-methoxyphenyl)carbene complex, the chromium-oxygen bond is about the same length as in the labile $(CO)_5Cr$-ether adducts[164] and therefore easily opened. Thus, metallacycles of this kind represent a stabilized form of the coordinatively unsaturated tetracarbonyl species. **125** reacts smoothly with the alkyne ester **126**, which is obtainable in two steps from methyl acetoacetate, to give the anthracene complex **127**. This compound is very sensitive toward oxidation, but easy to separate because of its sparing solubility; under CO pressure, it is quantitatively cleaved to give the aromatic ligand **128** and hexacarbonylchromium, which can be reused in the synthesis of the carbene complex. The anthracenyl ester **128** is a suitable intermediate in the preparation of 4-demethoxydaunomycinone **129** (Scheme 17).

7. Catalytic Reactions

Although the emphasis in this discussion is on the stoichiometric use of carbene complexes, the catalytic reactions will be considered in this final section, using some characteristic examples. Here, only those processes will be considered that are initiated by isolable, well-defined complex compounds.

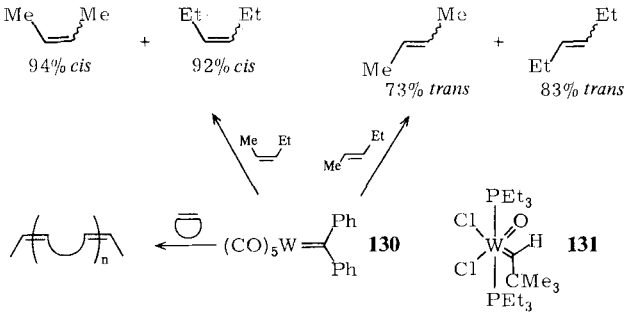
7.1. Olefin Metathesis

Ever since the discovery of metal-catalyzed alkylidene exchange in alkenes, i.e. of "olefin metathesis"[165,166], its mechanism

$$2\,RCH{=}CHR' \xrightarrow{\text{catalyst}} RCH{=}CHR + R'CH{=}CHR'$$

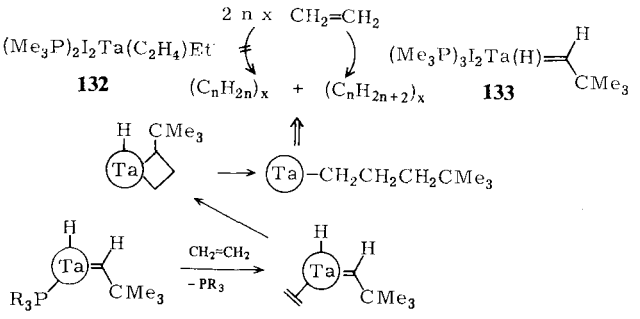
has been the object of controversial discussion. At present, the view is generally accepted that the key step involves bond formation between a carbene and an alkene ligand to form a metallacyclobutane[167]. This conclusion could be arrived at largely because of the fact that the isolable carbene complexes provided well-characterized starting materials, the catalytic effectiveness of which could be studied in model reactions. Compounds of tungsten, which is

known as a "metathesis-active" metal, proved especially useful. Whereas the methoxy(phenyl)carbene complex **23** only reacts with the more reactive cyclic olefins such as norbornene[168], giving a polymeric norbornene with an average molecular weight $\overline{M}_r$ of ca. 1.1×10^5, the diphenylcarbene complex **130** also reacts with open-chain alkenes[169–171]. In contrast to most conventional catalyst systems, a high stereoselectivity is observed. Thus, cyclic and acyclic *cis*-olefins give more than 90% *cis*-products. The configuration of *trans*-alkenes such as *trans*-2-pentene, however, is not so well preserved. In addition to the "Fischer-type" compounds, "Schrock-complexes", such as **131**, have also proven to be metathesis-inducing. However, Lewis acids have to be added in this case in order to achieve turnover numbers of ca. 50[172,173].



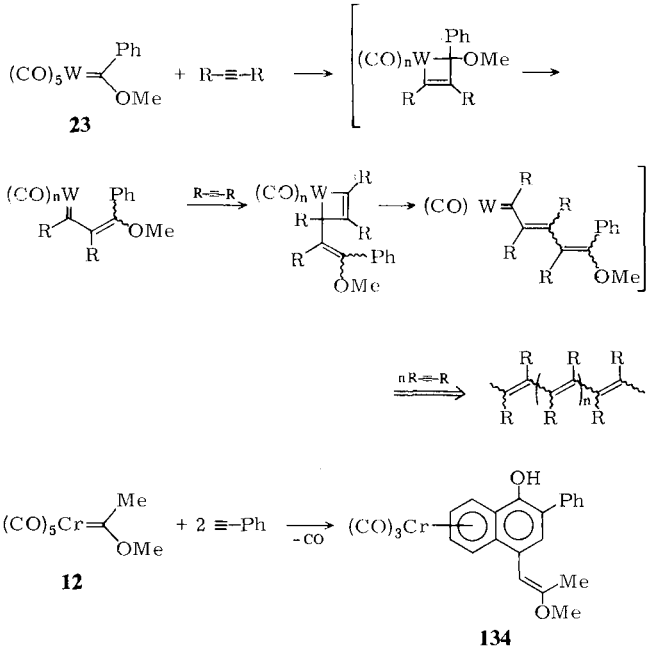
7.2. Polymerization of Alkenes and Alkynes

The Ziegler-Natta polymerization of alkenes is generally thought to be due to insertion of the olefin into a metal-alkyl bond[174,175]. This contrasts with a recently made suggestion that carbene-hydride complexes should be effective as catalysts[176]. Such species are known for tantalum and thus provided the opportunity to test this hypothesis[177,178]. Interestingly, it was observed that—in contrast to the alkene-alkyl compound **132**—the neopentylidene-hydride complex **133** is able to polymerize ethylene. After hydrolysis of the initial product alkenes and alkanes are obtained. The chain growth is explained by the formation of a metallacyclobutane which is opened to give the alkyl complex (Scheme 18).



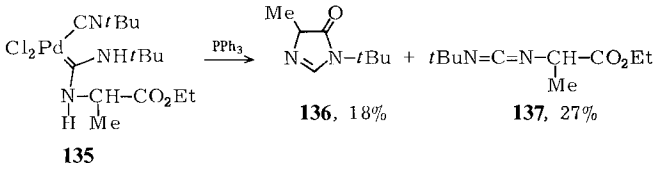
Scheme 18. A mechanism proposed for the polymerization of ethylene catalyzed by carbene-hydride complexes. (Ta) = $(R_3P)_2I_2Ta$.

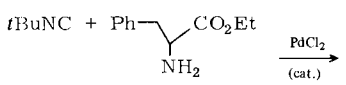
Carbenetungsten complexes of the "Fischer-type" have also proven to be effective catalysts in the polymerization of alkynes[179]. The reactions initiated by **23** or **130** proceed slowly but give comparatively pure products. Unbranched terminal alkynes give good yields (50—75%). Dialkylalkynes such as 2-butyne, whose polymerization by conventional catalyst systems is described only for isolated cases, react more poorly, as expected; characteristic $\overline{M}_r$ values are about 25000. In accord with the preferred mechanism of the olefin metathesis reaction, the chain growth is described by repeated addition of the alkyne to the metal-carbene bond to give the metallacyclobutene followed by its ring opening to give the alkenylcarbene complex. Coupling of two alkyne units with a carbene ligand and a carbonyl ligand to give the alkenylnaphthol **134** can also be explained in terms of repeated formation and opening of a metallacyclobutene[180].

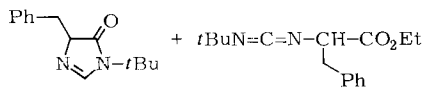


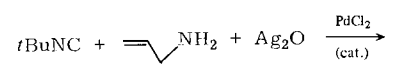
7.3. Synthesis of Heterocycles

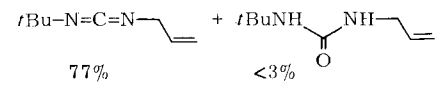
By introduction of an amino group, the carbene carbon is usually so stabilized that it can no longer be used in specific reactions. In the palladium series of complexes, however, diaminocarbene ligands, which can be synthesized by addition of α-amino acid esters or β-amino alcohols to coordinated isocyanides, have proven to be precursors of some N- and N,O-heterocycles, respectively[58]. Thus, the carbene ligand in **135** is cleaved by substitution with phosphanes or by oxidation and modified to give the imidazolone **136** or the carbodiimide **137**. The reaction can also be carried out directly starting with isocyanides and using catalytic amounts of palladium chloride. The main product resulting after oxidation with silver(I) oxide is the carbodiimide[181] or, if β-amino alcohols are used, the aminooxazole.

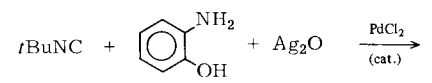


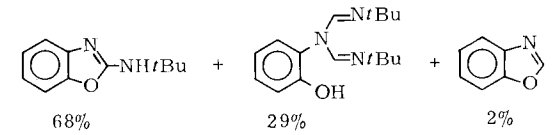












8. Outlook

Only two decades ago carbene complexes were still regarded as exotic compounds in organometallic chemistry. Today, numerous carbene complexes can be synthesized with various metals and with a broad range of substitution patterns. They offer a broad potential for synthetic use. In this review it has been shown that not only those reaction types are encountered which are transferable from "organic" carbene chemistry. On the contrary, by the additional interaction of ligands within the coordination sphere of the metal, the scope is enlarged to allow bond formation between specific ligands; so far, however, this has only been explored in individual cases. In particular, the cocyclization of carbene ligands with several other ligands or compounds, which has proven useful in the synthesis of natural products, promises to find broad application. Here, the metals show pronounced specificity, as shown by the chromium-induced formation of hydroquinone, so that the use of other metals should lead to further interesting results. Moreover, a "fine tuning" is possible by variation of the co-ligand sphere.

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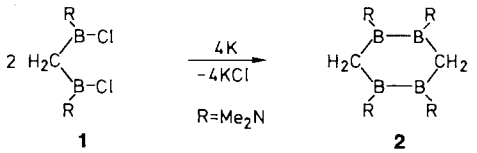
Synthesis and Structure of a 1,2,4,5-Tetraborinane**

By *Herbert Fisch, Hans Pritzkow,* and *Walter Siebert**

Dedicated to Professor Margot Becke on the occasion of her 70th birthday

Due to a deficiency of electrons, the derivatives of the B–C-compounds $(RB)_4(CR')_2$, $(RB)_4(CR')_2H_2$, and $(RB)_2(CR')_4$, with R, R′ = H, alkyl, exhibit carbaborane structures[1]. $(RB)_2(CR')_4$ is stabilized as a 1,4-diboracyclohexadiene derivative by electron donating substituents on the boron atoms, a stabilization that was first accomplished with the fluoro compound $(FB)_2(CR')_4$[2]. The stability of *cyclo*-organoborane/*nido*- or *closo*-carbaborane has been studied in detail by PRDDO calculations on $(RB)_2(CR')_4$, $(RB)_3(CR')_2$, and $(RB)_4(CR')_2$[3].

We report here a novel B_4C_2 ring **2**, stabilized by dimethylamino groups, whose parent compound $B_4C_2H_8$ is expected to have a *nido*-structure. The slightly air-sensitive compound **2** is formed upon dehalogenation of the



1 **2**

bis(aminoboryl) derivative **1**, obtained from bis(dichloroboryl)methane and $Me_3Si–NMe_2$, with Na/K alloy[4]. On the basis of the ^{1}H-NMR data [$\delta = 0.91$ (d, $J = 10.3$ Hz, 2H), 1.50 (d, 2H), 2.80 (s, 12H), 2.83 (s, 12H)], a planar ring can be ruled out. Neither the CH_2- nor the CH_3-signals coalesce below 105 °C (in [D_8]-toluene), thus indicating a relatively rigid conformation and strong (BN)-π-bonding. The ^{11}B-NMR signal at $\delta = 53.7$ is typical for a diborane containing alkyl- and Me_2N-substituents[6]. The isotopic pattern characteristic for four boron atoms appears at $m/z = 248$ ($M^{\oplus}$, 100%) in the mass spectrum. $M^{\oplus}/2$ is observed at $m/z = 124/125$ (50%). Preparative evidence for the 1,2-bis(dimethylamino)diborirane, the corresponding three-membered ring, could not be found.

1,2,4,5-Tetrakis(dimethylamino)-1,2,4,5-tetraborinane **2** crystallizes in the triclinic space group $P\bar{1}$ with two crystallographically independent, centrosymmetric molecules which differ only slightly from each other (Fig. 1)[7]. The ring lies in the chair-conformation. The angle between the

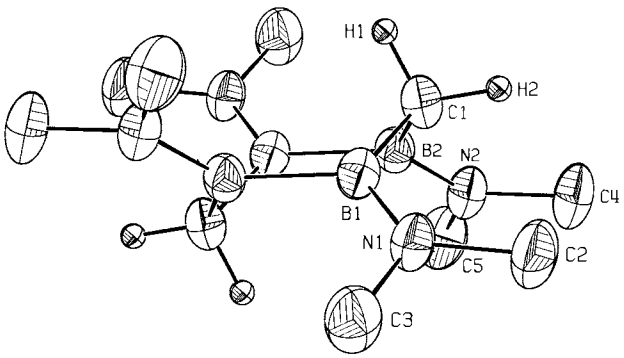


Fig. 1. ORTEP diagram of one of the two molecules of **2** in the crystal (vibration ellipsoids with 40% probability, for methylene-H atoms arbitrary; for sake of clarity the methyl-H atoms are omitted). Bond lengths [Å] and angles [°] (averaged values for both molecules, standard deviations 0.002 Å and 0.1°): B–B 1.711, C–B 1.590, B–N 1.405, N–C 1.457; B–C–B 105.5, C–B–B 113.3, C–B–N 122.2, B–B–N 124.0, C–N–C 111.3, B–N–C 124.1 [7].

plane through the four boron atoms and the plane through B1-C1-B2 is ca. 50°. The boron and nitrogen atoms are planar coordinated, whereby the boron atoms deviate slightly more from the respective planes (up to 0.05 Å). The angle of twist between the planes NBBC and BNC_2 is small (2—6°) so that a good π-interaction with a resulting short B-N distance is possible. The bond lengths in the ring correspond to the values for single bonds.

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A comparison with hexakis(dimethylamino)cyclohexaborane[8] and 2,3,5,6-tetrakis(dimethylamino)-1,4,2,3,5,6-dithiatetraborinane[9] shows that the B-B and B-N distances in all three compounds are equal and that the planarity of the XBB–NC_2 group is preserved. The cyclohexaborane, like the tetraborinane **2**, exhibits a chair-conformation, whereas the dithiatetraborinane adopts a twist-conformation.

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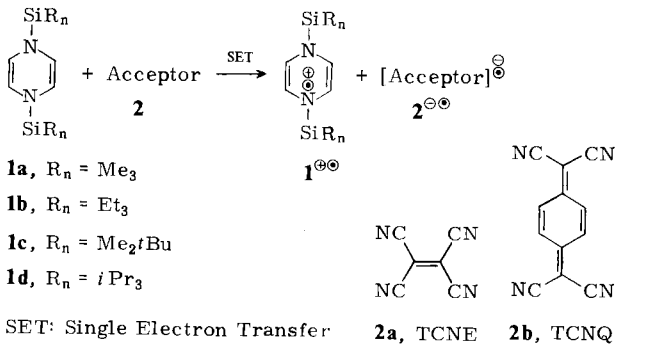
Isoelectronic Radical Ions from Single-Electron Transfer Reactions: Direct Observation of Persistent Solvent-Separated Radical Anion/Radical Cation Pairs**

By *Wolfgang Kaim**

The possibility of electron transfer mechanisms being involved in reactions of organic compounds with organometallic reducing agents has recently been discussed in the literature[1]. Although evidence indicating the involvement of such mechanisms has been reported on several occasions, some of the findings have been misinterpreted, particularly regarding the identity of the long-lived radical species observed[1,2]. The primary product of a "single electron transfer" (SET) between diamagnetic closed-shell reactants, the pair of oppositely charged radical ions, is generally very reactive owing to the instability of simple organometallic radical cations[3].

N-Silylated 1,4-dihydropyrazines **1** are electron-rich[4] reducing agents[5] forming stable radical intermediates[4,6]. We have now been able to observe both radical ions simultaneously on allowing **1** to react with the acceptors tetracyanoethylene (TCNE) **2a** or tetracyanoquinodimethane (TCNQ) **2b**.



This is the first *direct* evidence of thermal single-electron transfer involving main group organometallic reductants; earlier claims of this sort have proven invalid[2].

Variation of the organometallic component[4,7] shows that steric effects play an essential role, aside from electronic stabilization by the pyrazine system: the larger the substituents R on the silicon atoms, the more stable are the radical ion "pairs" in solution; in the case of the bis(triisopropylsilyl) compound **1d**, both species can be readily observed at room temperature (Fig. 1).

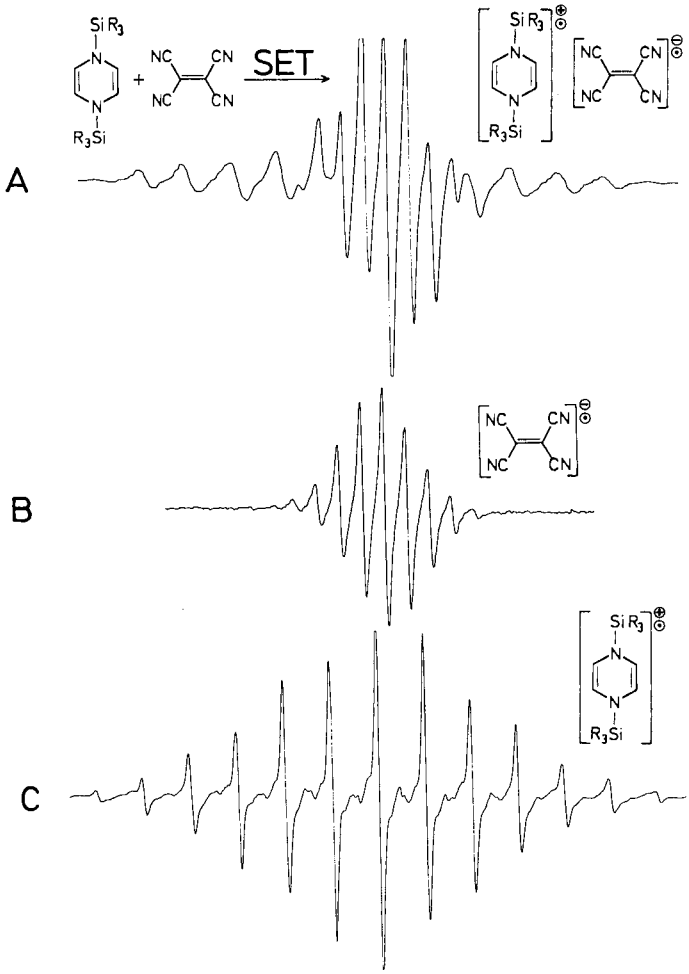


Fig. 1. According to the potential difference between **1d** ($E_{ox}=-0.35$ V) and TCNE **2a** ($E_{red}=+0.33$ V vs. SCE), single electron transfer occurs during the reaction in dichloromethane. The primary products, the radical ions $\mathbf{1d}^{\oplus\odot}$ and $\mathbf{2a}^{\ominus\odot}$, can be detected simultaneously as persistent solvent-separated ions; the ESR spectrum of the reaction solution (A) is a superposition of spectra of the components $\mathbf{2a}^{\ominus\odot}$ (B) and $\mathbf{1d}^{\oplus\odot}$ (C) [4]. Particularly characteristic is the loss of inversion symmetry in (A) because of the slightly different g factors of the components ($\mathbf{2a}^{\ominus\odot}$: $g=2.0029$; $\mathbf{1d}^{\oplus\odot}$: $g=2.033$); the line-broadening in (A) compared to (C) could arise through weak association.

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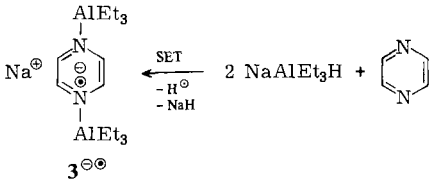
From the point of view of the pyrazine system, the direction of this electron transfer is reversed relative to that in the reaction of the oxidized pyrazine with organometallic reducing agents[8], e.g. to give $3^{\ominus\odot}$.



$3^{\ominus\odot}$

The occurrence of iso-π-electronic radical ions[9] such as $1^{\oplus\odot}$ and $3^{\ominus\odot}$ demonstrates the excellent suitability of the pyrazine system for studies of electron transfer phenomena.

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[7] Preparation by reductive silylation of pyrazine (^{1}H-NMR in $CDCl_3$/TMS). **1b**: yellow oil, b.p. 85°C/10^{-4} torr; $\delta \approx 0.7$ (m, 30H), 4.65 (s, 4H); **1c**: yellow crystals, subl. 80°C/10^{-4} torr; $\delta = -0.02$ (s, 12H), 0.98 (s, 18H), 4.62 (s, 4H); **1d**: yellow crystals, subl. 120°C/10^{-4} torr; $\delta = 1.13$ (pseudo-s, 42H), 4.78 (s, 4H).
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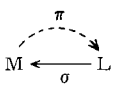
π-Back Bonding and Stability of the Oxidation States in Tetracarbonyldicyclopentadienyl-(μ-pyrazine)dimanganese(I) Complexes**

By *Renate Gross* and *Wolfgang Kaim**

Transition metals with low-spin d^6-configuration such as Fe^{II}, Ru^{II}, Os^{II} or Cr^0, Mo^0, and W^0 are capable of back-bonding with π-acceptor ligands L:



Characteristic of such complexes are intense MLCT (metal-to-ligand charge transfer) bands[1,2]—often in the visible region of the spectrum—and a typical, well documented[3] photochemistry. Support of an MLCT assignment, i.e., for an electron transition (Scheme 1) into a ligand π* orbital can be obtained by electrochemical and ESR studies[4].

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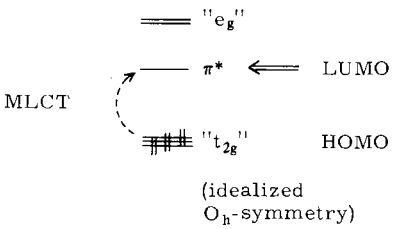
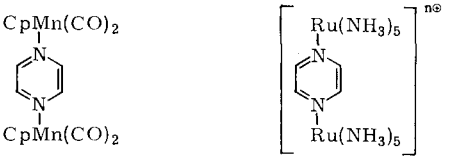


Scheme 1.

Few such studies have been carried out on manganese(I) complexes[5], even though the coordination chemistry of the fragment $MnCp(CO)_2$ is extensive, and has led to the stabilization of some unusual ligands[6,7].



1a, Cp = η^5-C_5H_5
1b, Cp = η^5-$C_5H_4CH_3$
1c, Cp = η^5-$C_5(CH_3)_5$

2, n = 4,5,6

In our effort to study organometallic analogues of the Creutz-Taube system **2**[8], we have prepared the binuclear pyrazine complexes **1**[9] and examined them both electrochemically and spectrocopically. A comparison with related Ru^{II}, Fe^{II}, and Cr^0 complexes reveals quite clearly the remarkable position of the Mn^I complexes (Table 1):

Table 1. MLCT absorption maxima E_{MLCT} [eV] and redox potentials $E_{ox/red}$ or peak potentials [d] [V vs. SCE] for μ-pyrazine complexes with low-spin d^6-metal fragments; pz = pyrazine.

Complex	E_{MLCT}	E_{ox}	E_{red}
2, n = 4 [8] [a]	2.27	+0.12	[b]
$\{pz[Fe(CN)_5]_2\}^{6\ominus}$ [10] [a]	2.45	≈0.0	[b]
$pz[Cr(CO)_5]_2$ [c]	2.41	+1.1 [d]	−1.05 [d]
1a [c]	1.94 2.14 [e]	+0.37 [d]	−1.36
1b [c]	1.88 2.12 [e]	+0.34 [d]	−1.37
1c [c]	1.80 2.03 [e]	+0.25 [d]	−1.40

[a] Measurements in water. [b] Not observed. [c] Absorption measurements in benzene [2] or toluene; cyclovoltammetry in dimethylformamide/0.1 M tetrabutylammonium perchlorate. [d] Peak potential for irreversible redox behavior (cyclovoltammetry, scan rate 100 mV/s). [e] Two bands due to lower symmetry [5].

- The Mn^I complexes **1** absorb at even longer wavelengths than the Ru^{II} compounds **2**[1,8]; this quantitative evidence of unusual π-back-bonding behavior may be related, e.g., to the stability of the corresponding N_2 complexes[7].
- Twofold coordination of $MnCp(CO)_2$ to pyrazine facilitates the reduction of the ligand by about 0.7 V.
- Acquisition of an electron affords relatively stable (Cp!) radical anion complexes (Fig. 1), whose ESR data confirm the ligand character of the singly occupied molecular orbital (Scheme 1)[4c]; however, a noticeable interaction already occurs with the coordinated metal fragments. From the relative size of the g factor of the radical anions ($g_{complex} < g_{electron} = 2.0023$), it can be de-

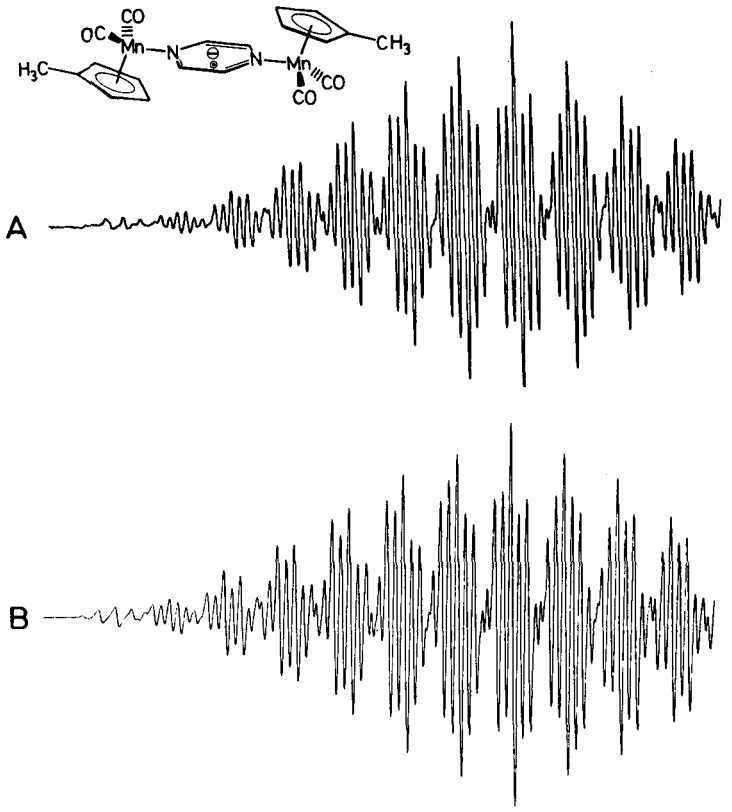


Fig. 1. Low-field section (A) of the ESR spectrum of complex $\mathbf{1b}^{\ominus\ominus}$ in THF, generated by reduction with potassium. Computer controlled spectra-synthesis (B) with the coupling constants [μT]: 227 (4 H), 865 (2 N), 747 (2 Mn) and with a line width of 60 μT; 275 theoretical lines, $g = 1.9997$.

duced[4d] that a further unoccupied orbital must be close-by; consistent with this, the compounds are very light-sensitive. Obviously, an effective photoreaction takes place from a state other than the MLCT excited state[5].

The oxidation of the complexes **1**, which should lead to a mixed valence system analogous to the Creutz-Taube ion **2**, n = 5, is dissociative under the electrochemical conditions employed—apparently due to electrocatalytic substitution by the solvent[11].

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[9] General procedure: $MnCp(CO)_2(THF)$, generated by irradiation of $MnCp(CO)_3$ in tetrahydrofuran (THF), is allowed to react with pyrazine in the molar ratio 3 : 1. After prolonged stirring at room temperature under exclusion of light, a blue coloration indicates formation of the binuclear complex **1**; after 1 d the solvent is removed in vacuo and the product worked-up by low-temperature column chromatography (Florisil, −30 °C). Unreacted $MnCp(CO)_3$ is first eluted from the column with toluene/hexane (4 : 1), then the reddish-brown mononuclear complex with toluene, and finally the binuclear product **1** with THF. The product **1** is recrystallized from THF/hexane; yield ca. 25% (**1a**, **b**) and 5% (**1c**), respectively. The dark crystals are sensitive towards light and air (quoted yields in the absence of light and air!). IR (THF; ν_{CO} [cm^{-1}]): **1a**: 1925, 1865; **1b**: 1928, 1860; **1c**: 1915, 1852. ^{1}H-NMR (C_6D_6): **1a**: $\delta = 4.00$ (s, 10 H), 7.18 (s, 4 H); **1b**: $\delta = 1.22$ (s, 6 H), 3.89 (ps, 8 H), 7.21 (s, 4 H); **1c**: $\delta = 1.40$ (s, 30 H), 7.24 (s, 4 H).
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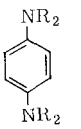
p-Phenylenediboranes: Mirror Images of *p*-Phenylenediamines?

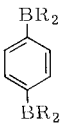
By *Wolfgang Kaim** and *Andreas Schulz*

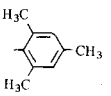
The *p*-phenylenediamines **1**, the prototypes for electron-rich organic compounds, can act as components of donor-acceptor complexes[1a], and their one-electron oxidation products, the radical cations, have been known[1b] as *Wurster's salts* for more than a century. The strong donor function of an amino group should find its counterpart in the acceptor capability of boryl substituents, and there are some relatively stable radical anions $BR_3^{\ominus\ominus}$[2]; in the case of boranes, however, complications can arise because of their sensitivity toward oxidation and their tendency to cleave BC bonds and to form *ate* complexes.



1

R = Alkyl, Aryl



2, R = 

3, R = Ph

4, BR_2 =

We have prepared the *p*-phenylenediboranes **2**–**4**[3] which are analogous to *p*-phenylenediamines and investigated their redox behavior both chemically and electrochemically. As in the case of simple boranes BR_3[2c], no reversible electrochemical reduction is observed with alkyl (**4**) and phenyl derivatives **3** (Table 1); however, introduction of the bulky dimesitylboryl substituents[4] precludes the aforementioned side reactions, ensures effective inter-

Table 1. Electrochemical reduction potentials *E* [V vs. SCE] of aromatic boranes [a].

	R_3B [b]		p-R_2B–C_6H_4–BR_2 [c]
R = Mesityl	−2.4 (r.)	**2**	−1.39 (r.) −2.08 (r.)
R = Phenyl	−2.12 (qr.) −3.08 (ir.)	**3**	−1.9 (ir.)
BR_2 = 9-Borabicyclo-[3.3.1]nonyl	—	**4**	−2.4 (ir.)

[a] The steps are designated as reversible (r.), quasi-reversible (qr.), or irreversible (ir.); cathodic peak potentials are given in the latter case. [b] Ref. [2c]: Pt electrode, THF, $nBu_4N^{\oplus}ClO_4^{\ominus}$ (0.2 M), potentials vs. $Ag/Ag^{\oplus}$ recalculated to potentials vs. SCE. [c] Glassy-carbon electrode, DMF, $nBu_4N^{\oplus}ClO_4^{\ominus}$ (0.1 M).

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action[4] of the unoccupied *p*-orbitals on the boron atoms with the π-system of the central benzene ring, and thus causes **2** to behave diametrically opposite to the *p*-phenylenediamines:

The cyclovoltammogram in dimethylformamide (DMF) shows two reversible reduction steps to the radical anion and to the dianion (Fig. 1); the separation of 0.69 V corresponds to a rather large radical formation constant of 5×10^{11}. The oxidation of **1** also occurs in two reversible steps, albeit with a somewhat smaller separation of 0.44 V[5].

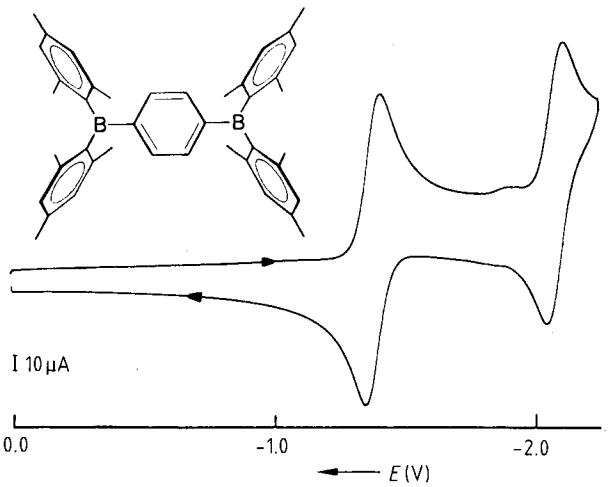

Fig. 1. Cyclovoltammogram (reduction) of *B,B,B',B'*-tetramesityl-*p*-phenylenediborane **2** in dimethylformamide (10^{-3} M).

The (negative) reduction potential of **2** is very high for a *p*-disubstituted benzene derivative (Table 1); the value of −1.39 V vs SCE is exceeded only by that of −0.57 V for *p*-nitrobenzene[6]. In comparison to benzene ($E_{red} = -3.42$ V[7a]), this signifies facilitation of the reduction by ca. 2.0 V; a similar difference of about 2.2 V exists between the oxidation potential of benzene (≈ +2.4 V[7b]) and that of **1** (≈ +0.25 V[5]).

Unfortunately, the ESR spectrum of the radical anion $\mathbf{2}^{\ominus\ominus}$ is no longer resolved due to the number 511875 (!) of theoretical lines ($g = 2.0025$). However, electron nuclear double resonance (ENDOR)[8] yields a largest ^{1}H-coupling of only 119 μT, which is assigned to the phenyl protons and indicates considerable delocalization of the unpaired electron. Once again, a comparable effect is only shown by the *p*-nitrobenzene system (a_H = 112 μT[9]).

These results illustrate quite convincingly that the acceptor dimesitylboryl[4] is only surpassed by the NO_2 substituent, both energetically as well as with respect to the delocalization of negative charge, and, despite their steric requirements, compounds like **2** or **3** should be suitable as components of donor-acceptor complexes.

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[3] Prepared from *p*-$BrMnC_6H_4MgBr$ and mesityl$_2$BF (**2**), Ph_2BBr (**3**) and 9-Borabicyclo[3.3.1]nonyl bromide (**4**). ^{1}H-NMR ($CDCl_3$/TMS): **2**: δ = 2.04 (s, 24H), 2.34 (s, 12H), 6.82 (s, 8H), 7.45 (s, 4H); **3**: δ = 7.19 (s, 4H), 7.41 (m, 8H), 7.74 (d, 8H), 7.80 (t, 4H); **4**: δ = 1.2–2.2 (m, 28H), 8.05 (s, 4H).

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Sequential Lithiation and Silylation of Stannocene**

By *Alan H. Cowley**, *Peter Jutzi**, *Franz X. Kohl*, *Jonathan G. Lasch*, *Nicholas C. Norman*, and *Ewald Schlüter*

It has been noted that the properties of Me_3Si-substituted cyclopentadienyl ligands are complementary to, yet distinct from, those of the more familiar $Me_5C_5^{\ominus}$ moiety[1]. The existing methodology for introducing the silylated ligands involves treatment of e.g. $(Me_3Si)_2C_5H_3Li$ with metal halides. We have now found a new route to polysilylated cyclopentadienyl compounds which starts from the parent metallocene.

Treatment of $(C_5H_5)_2Sn$ with *n*BuLi (molar ratio 1:2) in tetrahydrofuran (THF) at −78 °C affords 1,1'-dilithiostannocene[2], which can be quenched with Me_3SiCl to give $(Me_3SiC_5H_4)_2Sn$ **1**. Repeated treatments of this kind lead sequentially to 1,1',3,3'-tetrakis(trimethylsilyl)stannocene **2** and 1,1',2,2',4,4'-hexakis(trimethylsilyl)stannocene **3**.

$$(C_5H_5)_2Sn \xrightarrow[2)\ 2\,Me_3SiCl]{1)\ 2\,n\text{BuLi}} \underset{\mathbf{1}}{(Me_3SiC_5H_4)_2Sn} \xrightarrow[2)\ 2\,Me_3SiCl]{1)\ 2\,n\text{BuLi}}$$

$$[(Me_3Si)_2C_5H_3]_2Sn \xrightarrow[2)\ 2\,Me_3SiCl]{1)\ 2\,n\text{BuLi}} \underset{\mathbf{2}}{[(Me_3Si)_2C_5H_3]_2Sn} \qquad \underset{\mathbf{3}}{[(Me_3Si)_3C_5H_2]_2Sn}$$

The identification of **2** is based on elemental analytical and high-resolution mass spectroscopic data (M_r (calc.) 536.1381; M_r(found) 536.1392). Moreover, **2** can be prepared independently by reaction of $(Me_3Si)_2C_5H_3Li$ with $SnCl_2$. The NMR data for **2**[3] establish that, as in the case of lanthanide complexes[1], each η^5-cyclopentadienyl ring is 1,3-silyl substituted.

Compound **3**, which can also be synthesized from $(Me_3Si)_3C_5H_2Li$ and $SnCl_2$, was characterized by X-ray analysis (Fig. 1)[4]. Unfortunately, the crystals of **3** were only of poor quality, and hence the geometric parameters

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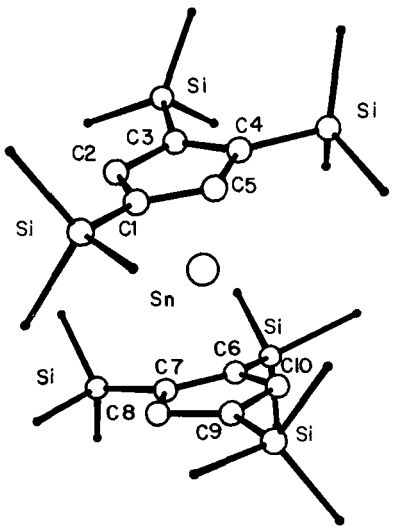

Fig. 1. Structure of **3** in the crystal. Selected bond lengths [Å]: C1-C2 1.42(3), C1-C5 1.49(4), C2-C3 1.56(3), C3-C4 1.54(3), C4-C5 1.48(4), C6-C7 1.57(4), C6-C10 1.54(3), C7-C8 1.50(2), C8-C9 1.54(2), C9-C10 1.53(4).

are not very accurate. However, two comments can be made about the structure: 1) The 1,2,4-substitution of the cyclopentadienyl rings is similar to that in the complexes $(Me_3Si)_3C_5H_2Li\cdot base$[5]; 2) the ring centroid-Sn-ring centroid angle is 162(2)°. This is considerably larger than the corresponding (average) angles in $(\eta^5\text{-}C_5H_5)_2Sn$ (145.8)[6] and $(\eta^5\text{-}Me_5C_5)_2Sn$ (144.1)[7].

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[3] **2**: ^{1}H-NMR (90 MHz, CH_2Cl_2); $\delta = 0.3$ (s, 36H, Me_3Si), 6.2 (br. s, 4H, H-4,4′,5,5′); 6.4 (br. s, 2H, H-2,2′). $^{13}C\{^1H\}$-NMR (20 MHz, CH_2Cl_2); $\delta = 119.4$ (s, C-4,4′,5,5′), 125.5 (s, C-2,2′), 26.2 (s, C-1,1′,3,3′).

[4] Monoclinic (from *n*-hexane), space group $P2_1$, $Z = 2$; $a = 10.566(8)$, $b = 18.24(3)$, $c = 10.621(4)$ Å, $\beta = 100.21(5)°$, $V = 2014$ Å^3; $\rho_{calc.} = 1.133$ g/cm^3; $2° \leq 2\theta \leq 50°$ ($Mo_{K\alpha}$, $\lambda = 0.71069$ Å), $\mu = 8.3$ cm^{-1}; 3417 independent reflections collected, of which 1673 ($I > 2.5\sigma(I)$) were used to solve (Patterson and difference Fourier) and refine (full matrix-least squares) the structure of **3**. Non-hydrogen atoms were all located and refined to $R = 0.132$. Further details of the crystal structure can by obtained from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, by quoting the depository number CSD 50931, the names of the authors, and the journal citation.

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High-Pressure Syntheses: The Henry Reaction**

By *Kiyoshi Matsumoto**

The Henry or nitroaldol reaction is one of the most important methods of CC bond formation, in particular since the nitro group of the nitroaliphatic compounds formed can be converted into other functional groups such as amines, alcohols, aldehydes, and ketones[1]. However, this reaction is sensitive to steric factors and "becomes less and less satisfactory the more substituents there are attached to the C atoms to be linked together"[2]. Yields are very low except for those reactions involving nitromethane itself, though a few important improvements have been reported[2,3]. Thus, Henry reactions of nitroalkanes with 2-methylcyclohexanone are unsuccessful, and higher nitroalkanes give low yields of nitroalcohols with 3- and 4-methylcyclohexanones[4]. We now report that some of these difficulties can be surmounted by the combined use of high pressure and nBu$_4$NF as catalyst[5,6].

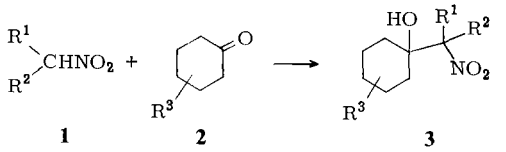

Table 1. Formation of nitroalcohols **3** [a] from nitroalkanes **1** and ketones **2** (9 kbar, 30°C, 4 d) [6].

R^1	R^2	R^3	Yield [%] [a]	B.p. [°C/torr] M.p. [°C]
H	H	2-CH_3	50 (0) [4])	68—69/2
		3-CH_3	61 (29 [4])	79—80/2
CH_3	H	2-CH_3	41 [b] (0 [4])	78—79/2
		3-CH_3	87 [c] (10 [4])	74—75/2
		4-CH_3 [d]	60 (14 [4])	73—75/2
C_2H_5	H	2-CH_3	40 (0 [4])	88—89/2
		3-CH_3	81 (5 [4])	84—85/2
		4-CH_3	89 (10 [4])	85—86/2
		[e]	86 (40 [7] 20 [8])	90—92/9
CH_3	CH_3	H	74 (45 [8])	56—57 [f]
		[e]	53 (19 [8])	66—70 [g]

[a] Yields not optimized. Correct elemental analyses obtained for all new nitroalcohols; all products gave satisfactory spectroscopic data (IR and ^{1}H-NMR spectra). Literature yields in parentheses. [b] 14% with piperidine as catalyst. [c] 52% with piperidine as catalyst. [d] 6 kbar, 30°C, 4 d. [e] Acetone was used as ketone. [f] Recrystallized from *n*-pentane. [g] Sublimed at 70—75°C (bath temperature)/9 torr.

The results are summarized in Table 1. Even 2-methylcyclohexanone affords moderate yields of the corresponding nitroalcohols, and with 3- and 4-methylcyclohexanones the yields are greatly improved[9]. n-Bu$_4$NF has proven to be a better catalyst than piperidine (see footnotes [b, c] to Table 1). Thus, the use of elevated pressure has extended the scope and potential utility of the Henry reaction.

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[**] This work was supported by the Japanese Ministry of Education.

[5] For a description of the high pressure apparatus employed in this study, see K. Matsumoto, A. Sera, T. Uchida, *Synthesis*, in press; most recent review on high pressure reactions: P. Welzel, *Nachr. Chem. Techn. Lab. 31* (1983) 148; W. J. le Noble, *Chem. Unserer Zeit 17* (1983) 152.
[6] Procedure: A mixture of the ketone **2** (16 mmol) and the nitroalkane **1** (24 mmol) is diluted with 1 M solution of nBu$_4$NF in tetrahydrofuran in a 10 mL Teflon capsule, which is then stored for 4 d at ca. 30 °C and 9 kbar. The reaction mixture is diluted with 97 mL benzene and 3 mL acetic acid and extracted several times with water to remove the catalyst. The organic layer is dried over $MgSO_4$. After removal of the solvent and unchanged starting materials under reduced pressure, the residue is either distilled in vacuo or recrystallized (see Table 1).
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Molecular Structure of a 1,3-Diphosphaallene: (2,4,6-tBu$_3$C$_6$H$_2$)P=C=P(2,4,6-tBu$_3$C$_6$H$_2$), a Phosphorus Analogue of Carbon Disulfide**

By *Hans Heinz Karsch**, *Hans-Ulrich Reisacher*, and *Gerhard Müller**

The current interest in (p-p)$_\pi$ bonding systems with elements of higher rows has only recently led to the isolation of phosphacumulenes **1** for the first time[1-3]. However, the structural parameters of these compounds are not yet known.

R–P=C=X

1a, X = O[1]; **1b**, X = NR[2]; **1c**, X = CR$_2$[3]

R–P=C=P–R **2**, R = 2,4,6-tBu$_3$C$_6$H$_2$

S=C=S **3**

R–P=P–R **4**, R = 2,4,6-tBu$_3$C$_6$H$_2$

The most recently synthesized 1,3-diphosphaallene **2**[4] is now the first example of a structurally characterized phosphacumulene (see also [4c]). Its structural parameters are particularly interesting for a comparison with those of carbon disulfide **3**[5] and of the diphosphene **4**[6].

The X-ray structure analysis of **2** (synthesized as described[4a], recrystallized from toluene, colorless air-stable crystals) indicates that in the crystal, isolated molecules are present[7]. Two RP groups are bonded to an almost linearly-coordinated C atom (Fig. 1). The P=C bonds (1.635(8) and 1.630(8) Å) are markedly shorter than isolated P=C bonds with an sp^2-hybridized C atom (1.68–1.72 Å[8]). This shortening presumably reflects the special electronic characteristics of the heteroallene system and the smaller bond radius of the sp-hybridized C atom.

In carbon disulfide **3**, the CS bond length (d(C=S) = 1.554(5) Å[9]) is ca. 0.06 Å shorter than in thiocarbonyl compounds[10]. For P=C and P≡C systems, the Pauling bond radii lead one to expect bond lengths of 1.67 and 1.53 Å, respectively[11]. The PCP angle of 172.6(5)° indicates a slight but, nevertheless, significant deviation from linearity; angular deformations of this magnitude frequently result from packing effects. However, inspection of molecular models suggests that in this case the angular contraction reduces the interactions between the extremely bulky 2,4,6-tBu$_3$C$_6$H$_2$ moieties. Their mutual orientation is almost orthogonal with respect to the PP axis and approach each other to a greater extent than in R–P=P–R, where they adopt *trans*-positions relative to the P=P bond[6]. This orthogonality of the P-substituents is an important criterion for describing the P=C=P bonding system as a heteroallene, since allenes exhibit comparable geometry. Notable deviations with respect to allenes occur, however, with the CPC angles (100.3(4) and 99.9(4)°), which are similar to those in diphosphenes[6] and diarsenes[12] and can be interpreted as arising from approximately sp-hybridized P atoms; the bonding of the substituents via one p orbital in each case then accounts for the small CPC angle[13].

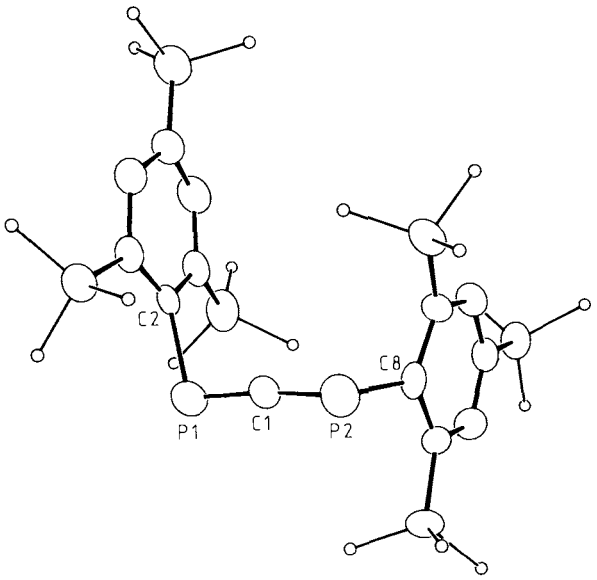

Fig. 1. Structure of **1** in the crystal (ORTEP; thermal ellipsoids 40%). The H atoms are omitted; the Me groups are shown with arbitrarily small radii. Plane angle C2P1P2/C8P2P1 = 83.0° [7].

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[**] Compounds of Main-Group Elements with Phosphinidene Substituents, Part 2. This work was supported by the Deutsche Forschungsgemeinschaft.—Part 1: [4a].

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[7] Crystal data: $C_{37}H_{58}P_2$, $M_r = 564.822$, monoclinic, $P2_1/n$, $a = 10.779(3)$, $b = 17.289(5)$, $c = 19.599(6)$ Å, $\beta = 90.19(2)°$, $V = 3652.4$ Å^3, $\rho_{calc.} = 1.027$ g/cm^3 for $Z = 4$, $\mu(Mo_{K\alpha}) = 1.36$ cm^{-1}, $F(000) = 1240$, $T = 21$ °C. 5086 independent reflections, 2833 of which unobserved ($F \leq 4\sigma(F_0)$); Syntex $P2_1$, $Mo_{K\alpha}$, $\lambda = 0.71069$ Å, ω-scan, $1 \leq \vartheta \leq 23°$). Direct methods (MULTAN 80). $R = 0.086$, $R_w = 0.066$, $w = k/\sigma^2(F_0)$, $k = 2.7$ in the last cycle, non-H atoms anisotropic (379 parameters), H atoms (calculated) constant (SHELX 76), $\Delta\rho_{max} = +0.33, -0.29$ e/Å^3. The rapid decrease in reflection intensity with increasing $\sin\vartheta/\lambda$, which arises from poor crystal quality and, in part, from disorder of the tBu groups, causes the large

standard deviations, the relatively high R values, and the unfavorable reflection to parameter ratio. Further details on the crystal structure investigation can be obtained from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, by quoting the depository number CSD 50922, the names of the authors, and the journal citation.

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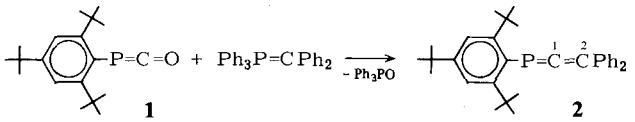
Phosphaallenes**

By *Rolf Appel**, *Peter Fölling*, *Bernhard Josten*, *Mustafa Siray*, *Volker Winkhaus*, and *Falk Knoch*

Dedicated to Professor Margot Becke on the occasion of her 70th birthday

So far, the only known representatives of the heterocumulenes R–P=C=X are those with X = NR'[1] and O[2], as well as the 1-phosphaallene **2** (X = CPh_2) recently described by *Yoshifuji* et al.[3]. We now report an independent synthesis of **2** using phosphaketene **1** and diphenylmethylenetriphenylphosphorane, an approach based on analogy to the Wittig reaction[4].



1 **2**

The IR and NMR data of **2** (m.p. = 165 °C) are consistent with the values given in [3] and fit the structure determined by X-ray diffraction studies (Fig. 1)[5].

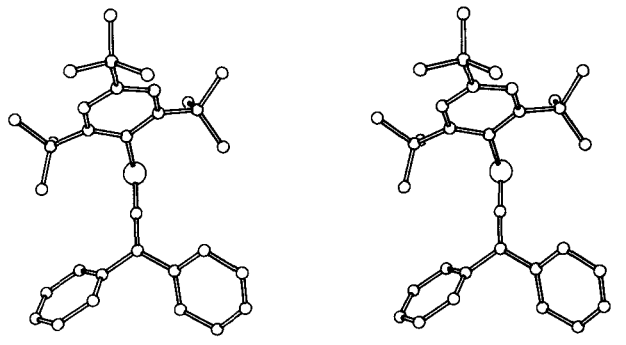
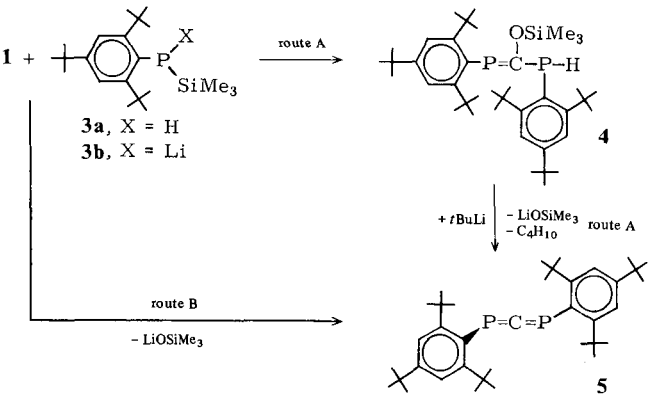


Fig. 1. Stereoscopic projection of the molecular structure of **2** in the crystal [5].

The phosphaketene **1** can also be used for the synthesis of the 1,3-diphosphaallene **5**. Addition of the silylphosphane **3a** to **1** (route A) leads initially to the isolable diphosphapropene **4**, which undergoes cleavage of lithium trimethylsilanolate with *tert*-butyllithium to afford the 1,3-diphosphaallene **5**[6]. By analogy to the carbodiphosphoranes[7], **5** can also be described as a carbodiphosphane. Alternatively, **5** can also be obtained directly via a Peterson olefination[8] by reaction of the lithium phosphide **3b** with **1** (route B)[6].



Because of the steric hindrance of the 2,4,6-tri-*tert*-butylphenyl substituents, **5** is so stable towards air and moisture that it can be purified by column chromatography. The composition and structure of the 1,3-diphosphaallene are based on the elemental analysis, a determination of the molecular mass, as well as MS and NMR data[9–11]. The synthesis of phosphaallenes **2** and **5** provides new evidence for the relationship between the PC and CC double bonds.

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[**] Low-Coordinated Phosphorus Compounds, Part 32.—Part 31: R. Appel, K. H. Dunker, E. Gaitzsch, T. Gaitzsch, *Z. Chem.*, in press.

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[3] M. Yoshifuji, K. Toyota, K. Shibayama, N. Inamoto, *Tetrahedron Lett. 25* (1984) 1809.

[4] Preparation of **2**: **1** (3.04 g, 0.01 mol) is placed in 80 mL anhydrous toluene and a solution of (diphenylmethylene)triphenylphosphorane (4.28 g, 0.01 mol) in 140 mL benzene added dropwise under an inert gas atmosphere with ice cooling. Subsequently the mixture is stirred for 3 h at room temperature. The solution is then evaporated to dryness and the residue purified by column chromatography (silica gel, hexane). Yield: 1.36 g (30%); m.p. = 165 °C.

[5] Molecular structure of **2**: Monoclinic, $P2_1/n$, a = 1097.9(3), b = 1730.8(4), c = 1458.0(4) pm, β = 90.06(2)°, V = 2770.6 × 10^6 pm^3, ρ_{calc} = 1.09 g/cm^3, Z = 4. Direct methods (SHELXTL), 2664 reflections, R = 0.078 (R_w = 0.070). Bond angles [°]: C_{aryl}PC1 104, PC1C2 167, torsion angle: C_{aryl}PC1C2 172; bond lengths [pm]: PC1 163, C1C2 131 (aryl = 2,4,6-tri-*tert*-butylphenyl). Further details on the crystal structure analysis can be obtained from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, by quoting the depository number CSD 50913, the names of the authors, and the journal citation.

[6] Preparation of **5** (route A): **4**: To a solution of **1** (1.52 g, 5 mmol) in 15 mL toluene is added dropwise an equimolar amount of silylphosphane **3a** (1.75 g, 5 mmol) at room temperature under an inert gas atmosphere. After 30 min, ca. 30 mL acetonitrile is added and the mixture cooled on an ice bath; the diphosphapropene **4** precipitates out and is washed with acetonitrile. Pale yellow crystals are obtained, yield: 2 g (61%), decomp. = 142 °C. $^{31}P\{^1H\}$-NMR (32.19 MHz, C_6D_6, standard 85% H_3PO_4): δ = −46.0 (dd, ^2J(P,P) = 66.3, ^1J(PH) = 220.6 Hz; P=C–*P*), 171.2 (dd, ^2J(P,P) = 66.3, ^3J(P,H) = 20.1 Hz; *P*=C–P); ^{1}H-NMR (90 MHz, C_6D_6):

$\delta = 0.22$ (s, $Si(CH_3)_3$), 1.35–1.73 (*t*Bu), 6.04 (dd, $^1J(P,H) = 220$, $^3J(P,H) = 20$ Hz; P*H*), 7.47–7.62 (aromat.); $^{13}C\{^1H\}$-NMR (20.0 MHz), $CDCl_3$): $\delta = 1.6$ (d, $^4J(P,C) = 2.9$ Hz; $Si(CH_3)_3$), 31–38 (*t*Bu), 121–156 (aromat.), 192.7 (dd, $^1J(PC) = 39.5$, $^1J(PC) = 90.8$ Hz; P=*C*–P). MS (20 eV/110°C, selected peaks): *m/z* 597 ($M^{\oplus} - t$Bu), 540 ($M^{\oplus} - 2t$Bu), 451 ($M^{\oplus} - 2t$Bu–$OSi(CH_3)_3$), 319 (arylPCP$^{\oplus}$), 276 (arylP$^{\oplus}$).—**5**: To a solution of **4** (2 g, 3 mmol) in 40 mL ether is added dropwise an equimolar amount of a 1.5 M solution of *tert*-butyllithium at −60°C, the contents of the flask mixed well and then warmed rapidly to +30°C. The solution becomes red. After addition to trimethylsilyl chloride to remove the base formed in the reaction and concentration of the reaction solution, the product is purified by column chromatography (silica gel, hexane) and recrystallized from hexane; m.p. = 202–204°C, yield: 0.81 g (48%).

Preparation of **5** (route B): **3b** (2.5 mmol) in 8 mL ether is added to a stirred solution of **1** (750 mg, 2.5 mmol) in 5 mL toluene. When the reaction ceases (30 min), 2.5 mmol trimethylsilyl chloride is added and the mixture stirred for 15 min. Undissolved residues are filtered off and the solvent removed using an oil pump. The residue is then taken up in benzene, and precipitation with acetonitrile gives 0.49 g **5** (35%).

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[9] MS (70 eV): *m/z* 564 ($M^{\oplus}$, 3%), 507 ($M^{\oplus} - t$Bu, 43%); ^{31}P-NMR (32.2 MHz, C_6D_6, 25°C): $\delta = +141.2$; ^{1}H-NMR (90 MHz, CD_2Cl_2, 25°C): $\delta = 1.25$ (br. s), 7.25 (s); ^{1}H-NMR (CD_2Cl_2, −40°C): $\delta = 1.0$ (s, *o*-*t*Bu), 1.2 (s, *p*-*t*Bu), 1.55 (s, *o*-*t*Bu), 7.25 (d, aryl); ^{13}C-NMR (20 MHz, $CDCl_3$, 25°C): $\delta = 276.2$ (t, $J(PC) = 58$ Hz).

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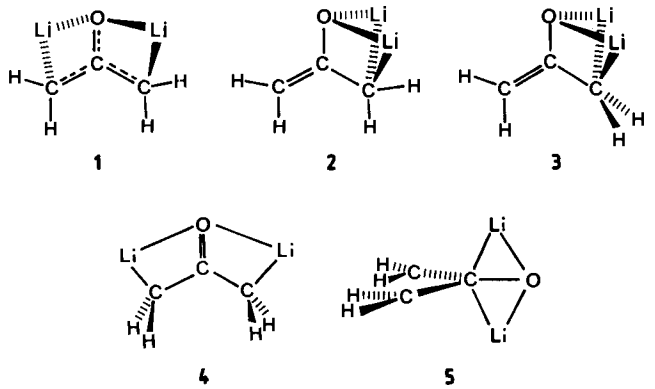
The ab initio Calculation of the Structure of 1,3-Dilithioacetone**

By *Alexander J. Kos, Timothy Clark,* and *Paul von Ragué Schleyer**

In cases where enolate anions react sluggishly, the reactivity and the nucleophilicity of the α-carbon atoms can be enhanced greatly by a second metallation. Hence, α,α′-keto dianions (in reality, dimetalated intermediates) are often employed in synthesis[1]. An NMR investigation[2] of the dilithium salt of the dibenzyl ketone dianion showed the high negative charges at the two benzylic C atoms typical of "Y-conjugated" systems[2]. We report here ab initio calculations with the split-valence 3-21G basis set[3] on the α,α′-keto dianion salt prototype, 1,3-dilithioacetone.



With the assumption that the Li atoms bridge the O and α-C atoms, there are two possible structures for the monomer. Structure **1** is chiral (C_2 point group symmetry) and has two enol moieties[4] and equivalent terminal C atoms. The lithium cations bridge above and below the dianion molecular plane, and some twisting of the CH_2 groups results (Fig. 1). This "opposite side" arrangement of two Li atoms, which is also found in several dilithiated conjugated hydrocarbon systems[5,6], is more favorable electrostatically (lower dipole moment) than the alternative with both Li atoms on the same side of the dianion moiety. Isomer **2** exhibits a different double bridging arrangement with both Li atoms attached to the same α-C atom. This C atom becomes much more negative than the α′-C atom, which is more olefin-like. The ab initio calculations (Table 1) indicate that **1** is 13.9 kcal/mol more stable than **2**. All the C, O, and H atoms in **2** lie in the same plane; this favors charge delocalization. Rotation of the carbanionic center by 90° gives isomer **3**, which has reduced conjugation. Nevertheless, only a small energy disadvantage results; **3** is 4.2 kcal/mol less stable than **2**. The loss of conjugation in **3** is partially compensated by the electrostatically more favorable orbital orientation at C_α. This is characteristic of 1,3-dilithium doubly bridged structures and has already been discussed in detail for other systems[7].

Complete removal of the Y-conjugation in **1** by 90° rotation of both CH_2 groups (isomer **4**) costs 33.1 kcal/mol. This high energy precludes the possibility of racemization of chiral α,α′-dilithio ketone derivatives by simultaneous rotation of both C–C bonds. Racemization involving exchange of Li atoms may occur instead through structures like **5**, which retain Y-conjugation. The energy difference between **1** and **5** is calculated to be only 16.3 kcal/mol.

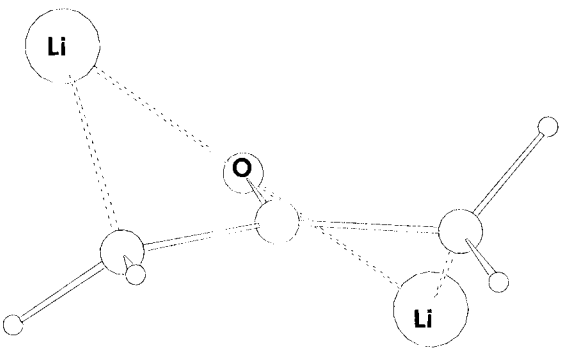


Fig. 1. 3-21G Optimized structure of 1,3-dilithioacetone **1**. Bond lengths [Å]: C–C 1.400; C–O 1.407; C–H 1.073 (*exo*), 1.083 (*endo*). Bond angles [°]: CCO 114.6; CCC 130.7; CCH 119.3 (*exo*), 116.8 (*endo*). Dihedral angles [°]: CCOLi 38.4; OCCH 186.9 (*exo*), 40.3 (*endo*).

Table 1. Calculated 3-21G energies for 1,3-dilithioacetone isomers **1**–**5**.

Isomer	E_{tot} [a.u.]	E_{rel} [kcal/mol]
1	−204.57903	0.0
2	−204.55693	13.9
3	−204.55019	18.1
4	−204.52317	33.1
5	−204.55306	16.3

The geometry of **1** corresponds remarkably well with the X-ray structure of 1,3-dilithiodibenzyl ketone[8]. The pre-

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ferred locations of the Li atoms are the same. The main differences between **1** and the X-ray result can be attributed to the presence of the coordinating tetramethylenediamine (TMEDA) molecules in the experimental structure[6]. The lower lithium coordination in **1** is reflected by the shorter Li–O and Li-α-C distances (0.1 and 0.4 Å, respectively). In addition, the C–O bond in **1** is 0.07 Å longer than that in the X-ray structure of 1,3-dilithiobenzyl ketone.

The experimentally observed structures of mono-enolate anions correspond to dimers and tetramers without Li–C interactions[4b,9]. In contrast, 1,3-lithium bridging between C and O atoms is found to be structure- and reactivity-determining in α,α′-keto dianions[8].

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Structure of a "Y-Conjugated" Dilithium Salt of an α,α′-Keto Dianion: 1,3-Dilithiodibenzyl Ketone-$(Me_2NCH_2CH_2NMe_2)_2$**

By *Hans Dietrich**, *Waruno Mahdi*, *Dieter Wilhelm*, *Timothy Clark*, and *Paul von Ragué Schleyer*

Although the enolates commonly used in syntheses are usually regarded as anions, their structures are complex and involve counterions and aggregated clusters[1]. Consideration of organoalkali metal structures as they really are, rather than as oversimplified models, is necessary to understand their reactivity and stereochemistry as well as the selectivity of their reactions[2]. We report here the first X-ray structure analysis of a monomeric dilithium salt of an α,α′-keto dianion. Both the position of the lithium counterions and the geometry of the carbodianion moiety are of interest. The ab initio structures of the parent Y-conjugated[3] system, 1,3-dilithioacetone, have been reported[4]. We compare here the experimental results on 1,3-dilithiodibenzyl ketone **1** with those obtained by MNDO calculations (Fig. 2)[5]; the preparation and NMR spectra of **1** and MNDO calculations on the corresponding dianion have already been discussed[6].

The X-ray structure of **1**[7] shows that the benzyl groups adopt *exo,exo* orientations, in agreement with the MNDO results on the dianion, but not with the results of NMR measurements in tetrahydrofuran (THF), which indicate a 65% *exo,endo*- and 35% *exo,exo*-mixture[6]. Both phenyl groups are twisted ca. 20° in opposite directions out of the plane of the central atoms; the MNDO findings indicate 21° for the dilithium salt (Fig. 2) and nearly the same value in the dianion[6]. Comparison of Figures 1 and 2 indicate that the X-ray and MNDO structures agree very well in their general features. As in the case of the parent system[4], other alternatives were examined calculationally, but were found to be less stable. With approximate C_2 symmetry, the dilithium salt is chiral, which may be significant in synthetic applications.

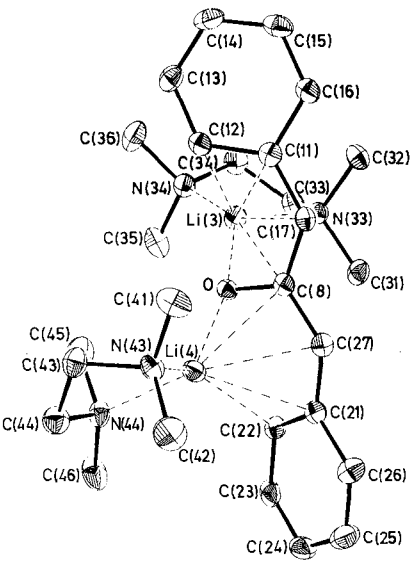

Fig. 1. Structure of 1,3-dilithiobenzyl ketone·$(TMEDA)_2$ in the crystal. The hydrogen atoms have been omitted. Important bond lengths [Å]: C(8)–O 1.334(1), C(8)–C(17) 1.413(2), C(8)–C(27) 1.402(2), C(11)–C(17) 1.424(2), C(21)–C(27) 1.434(2), C(11)–C(12) 1.423(2), C(21)–C(22) 1.433(2), C(12)–C(13) 1.386(2), C(22)–C(23) 1.395(2), C(13)–C(14) 1.376(2), C(23)–C(24) 1.381(2), C(14)–C(15) 1.388(2), C(24)–C(25) 1.391(2), C(15)–C(16) 1.374(2), C(25)–C(26) 1.375(2), C(16)–C(11) 1.430(2), C(26)–C(21) 1.421(2); Li(3)–O 1.849(2), Li(4)–O 1.870(2), Li(3)–C(12) 2.469(2), Li(4)–C(22) 2.425(2), Li(3)–C(11) 2.653(2), Li(4)–C(21), 2.505(2), Li(3)–C(17) 2.731(2), Li(4)–C(27) 2.550(2), Li(3)–C(8) 2.150(2), Li(4)–C(8) 2.415(2).

The C–O bond is lengthened due to coordination with the two Li atoms. The C–O distance of 1.334 Å (X-ray analysis, 117 K) is comparable to that found in aggregated lithium enolates[1] and phenolates[8,9]. The MNDO value for **1** (1.337 Å) is in good agreement with the experimentally determined value, in contrast to the shorter length calculated for the dianion (1.247 Å)[6]. The distances between the carbonyl and the benzylic carbon atoms (average 1.408 Å) are slightly shorter than those between the benzyl carbon atoms and the phenyl rings (1.429 Å). The lengths

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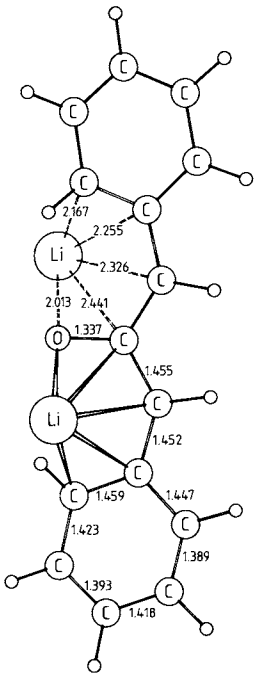

Fig. 2. Calculated (MNDO) structure of 1,3-dilithiodibenzyl ketone **1** (bond lengths in [Å]).

of these bonds in the calculated and experimental structures indicate the importance of conjugation in the dilithium compound.

The two Li atoms, each solvated by tetramethylethylenediamine (TMEDA), occupy bridging positions on opposite sides of the α,α'-keto dianion system. In addition to the strong coordination to oxygen (d(Li–O) = 1.86 Å), each Li atom is in close contact with four C atoms (Figs. 1 and 2). The LiC distances determined at 117 K by X-ray crystal structure analysis range between 2.42 and 2.73 Å.

The structure of **1** can be regarded as consisting of two fused enolate units with a common C–O bond. The lithium enolate units then correspond to the bridged form of acetaldehyde lithium enolate, which is indicated by ab initio calculations to be slightly less stable than the structure with a linear C–O–Li linkage[10]. This bridged form has not been observed for monoenolate aggregates, but is clearly favored for "dienolates"[4].

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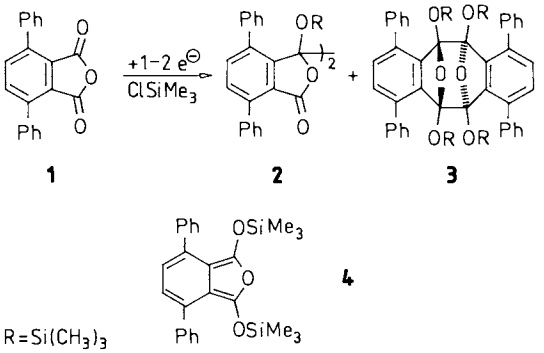
1,4,7,10-Tetraphenyldibenzo[*a*,*e*]cyclooctene-5,6,11,12-tetrone from 3,6-Diphenylphthalic Anhydride**

By *Theodor Troll**, *Georg W. Ollmann*, and *Helga Leffler*

Electrochemical reduction of *N*-phenyl- and *N*-methylphthalimide under aprotic conditions in the presence of trimethylchlorosilane leads to formation of 1,3-bis(trimethylsiloxy)isoindoles[1,2]. The reaction offers an extremely facile entry to 1,3-bis donor-substituted isoindoles[3]. Transfer of this reaction to phthalic anhydride affords exclusively bislactone ethers[1].

In the reduction of 3,6-diphenylphthalic anhydride **1** under the same conditions, however, we obtained, in addition to 4,7-diphenyl-3-hydroxyphthalide (7% yield) and the dimers **2** (34%, two diastereomers), the acetal **3**.



Reduction of **1** at the potential E^1 ($E_{1/2}=-1.32$ V vs. SCE, reversible formation of the radical anion) leads to isolation of **3** in 13% yield; at the potential E^2 ($E_{1/2}=-2.10$ V, reversible formation of the dianion), the yield increases to 25%. A reductive cyclization of **2** can be ruled out, since no reduction step was found in the potential range available. Hence, a bis donor-substituted isobenzofuran **4** has been obtained for the first time as an intermediate; previously, only 1-alkoxyisobenzofurans have been described[4].

Presumably **3** adopts the sterically more favorable configuration with *anti*-oxygen bridges, as in the dimeric parent compound[5]. No distinction could be made by complexation with NMR shift reagents. Potassium fluoride in ace-

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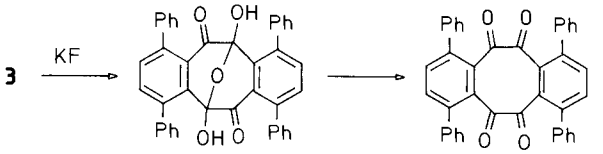
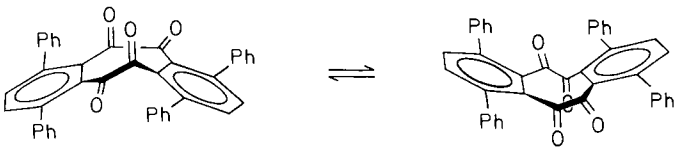
tonitrile converts **3** into **5**, which undergoes acid-catalyzed dehydration to yield the tetraketone **6**, the first member of this class of compounds[6].



5 **6**

Of note is the similarity between the UV spectra of **5** and **6** (Table 1). The two additional carbonyl groups in **6** effect practically no shift of the absorption maximum. The position of the long-wavelength maximum of **6** is consistent with that of 1,2-dicarbonyl compounds having orthogonal carbonyl groups[7,8]. On the basis of these data, the eight-membered ring adopts a twisted boat conformation. Two carbonyl groups are coplanar and hence are able to undergo conjugation with the neighboring terphenyl system; the two remaining carbonyl groups are perpendicular to this plane and are arranged parallel to each other. Inspection of a molecular model indicates that the change in



6a **6b**

conformation from **6a** to **6b** proceeds via pairwise exchange of carbonyl groups. For tetrahydrodibenzo[*a,e*]cyclooctene and some of its derivatives, a twisted boat conformation has been detected[9].

This conformational change, which proceeds rapidly even at room temperature, is also apparent from the ^{13}C-NMR spectrum, which up to $-80\,^{\circ}C$ displays only one signal for the carbonyl carbon atoms (Table 1). An X-ray structure analysis of **6** was unsuccessful because of the small number of observed reflections.

Table 1. Melting points and spectroscopic data for **3**, **5**, and **6**. ^{13}C-NMR: **3** and **6** in $CDCl_3$, **5** in CD_2Cl_2. UV: in CH_2Cl_2.

Comp.	M.p. [°C]	IR [cm^{-1}]	^{13}C-NMR (δ-values)	UV, λ_{max} [nm] ($\lg\varepsilon$)
3 [a]	322–324	no C=O	0.0 ($SiCH_3$) 105.0 ($C(C_2O_2)$) 126.5–141.0 (Aryl-C)	265 (4.8) 245 (4.7)
5 [b]	252–254	3440 (OH) 1725 (C=O)	96.8 ($C(C_2O_2)$) 126.5–143.5 (Aryl-C) 187.3 (C=O)	310 (3.5) 231 (4.4)
6 [c]	264–267	1720 and 1780 (C=O)	122.3–142.3 (Aryl-C) 192.1 (C=O)	303 (4.1) 229 (4.6)

[a] Anhydrous acetonitrile (ca. 60 mL), Et_4NCl (0.3–0.4 M), and $ClSiMe_3$ (5.0 mL, 39.5 mmol) are placed in a divided cell. At a potential of -2.2 V ($Ag/AgNO_3$), **1** (2.0 g, 6.6 mmol) is added portionwise ($i = 300$–400 mA). Aqueous work-up and low pressure column chromatography (50 g silica gel, CH_2Cl_2) lead to 745 mg (25%) **3** (1st fraction). Subsequent fractions contain the dimer **2**. [b] **3** (860 mg, 0.96 mmol) and KF (2.0 g) are stirred in acetonitrile for 5 d at room temperature. Hydrolysis and extraction with CH_2Cl_2 lead to 510 g **5** (90%). [c] A mixture of **5** (270 mg, 0.46 mmol), 4 g molecular sieve (4 Å, heat-dried), and ca. 50 mg *p*-toluenesulfonic acid in 100 mL toluene are refluxed for 5 d. After addition of Na_2CO_3 the solid is filtered off and washed with CH_2Cl_2. Removal of the solvent leaves 165 mg **6** (63%).

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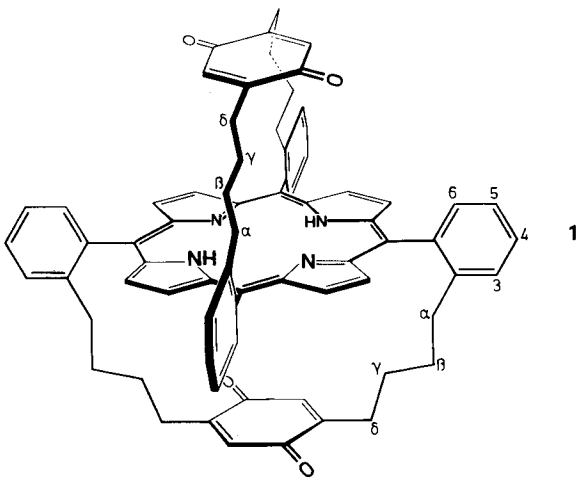
Synthesis of a Porphyrin Sandwiched between Two Parallel *p*-Benzoquinone Units

By *Jürgen Weiser* and *Heinz A. Staab**

Because of the considerable biochemical importance of electron-transfer reactions between porphyrins and *p*-benzoquinones, various intramolecular porphyrin-quinone systems have recently been synthesized in order to study the spatial requirements of such reactions[1]. In most cases, however, the covalent linkage between porphyrin and quinone involves either one single chain or two relatively long heteroatomic bridges, neither systems leading to porphyrin-quinone systems of well-defined geometry. In view of these studies, we wish to report on compound **1**, whose synthesis we began independently[2] in connection with our work on intramolecular charge-transfer interactions. In **1** a porphyrin is sandwiched between two *p*-benzoquinone units which, due to four hydrocarbon bridges, are kept in a fairly rigid arrangement above and below the center of the porphyrin moiety.



1

For the synthesis of **1**, the key precursor was 2,2′-[2,5-dimethoxy-1,4-phenylenebis(tetramethylene)]dibenzaldehyde **2**, which was prepared in the following way: 3,3′-

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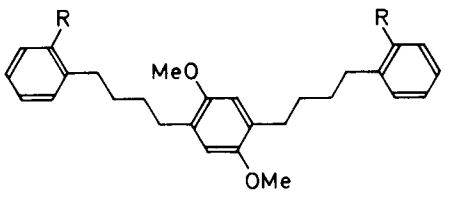
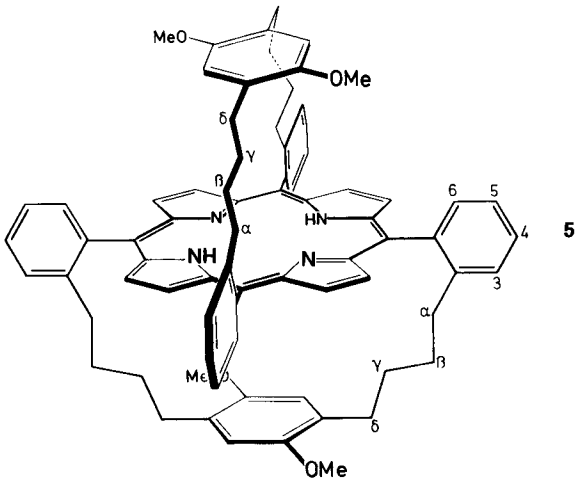
(2,5-dimethoxybenzene-1,4-phenylene)di-1-propanol[3] was oxidized (pyridinium chlorochromate, dichloromethane, 3 h, 20°C; 68% yield) to the corresponding dialdehyde (m.p. = 85–87°C)[4]. Wittig reaction with (2-methoxycarbonylbenzyl)triphenylphosphonium bromide (MeONa, MeOH, 60°C; 65%) yielded dimethyl 2,2'-[2,5-dimethoxy-1,4-phenylenebis(3-butenylene)]dibenzoate (*Z/E* mixture)[4], which was hydrogenated (Pd/C, methanol/ethyl acetate; quantitative) to the diester **3** (m.p. = 79-81°C)[4]. Reduction ($LiAlH_4$, tetrahydrofuran, 3 h reflux; 92%) led to the dialcohol **4** (m.p. = 128–130°C)[4], oxidation of which (pyridinium chlorochromate, dichloromethane, 3 h, 20°C; 90%) afforded dialdehyde **2** (m.p. = 90-92°C)[4].



2 : R = CHO
3 : R = COOMe
4 : R = CH_2OH

By analogy to the synthesis of tetraphenylporphyrin (TPP)[5], **2** was allowed to react with pyrrole (molar ratio 1 : 2, 4 h) in boiling propionic acid. Not unexpectedly, considering the bifunctionality of **2**, the majority of products of this reaction were oligomers and polymers which, however, could be separated on the basis of their insolubility and by chromatography (silica gel, toluene). Thin layer chromatography of the porphyrin fraction (silica gel, toluene/cyclohexane, 3 : 1) revealed that three different products, corresponding apparently to the three modes of condensation[6], are present. By repeated column chromatography (silica gel, toluene/cyclohexane, 3 : 1), fraction A ($R_F \approx 0.27$) was obtained pure (yield ca. 0.1%), whereas of the other two fractions, B and C, only the latter ($R_F \approx 0.15$) could be enriched to about 95% purity (yield ca. 0.5%)[7].

Compound A forms violet microcrystals (m.p. = 267-269°C, from dichloromethane/methanol). The elemental analysis, absorption spectrum (very similar to that of TPP), and mass spectrum [$m/z = 1106$ ($M^{\oplus}$, 100%), 1092 (8), 1091 (8), 1079 (16), 1078 (19), 553 ($M^{\oplus}/2$, 40)] are strongly indicative of a doubly bridged porphyrin. Furthermore, the ^{1}H-NMR data reveal that, out of the three isomeric structures, A has indeed structure **5** in which the two bridges diagonally link two opposite *meso*-positions of the porphyrin and, consequently, are arranged on either side of the porphyrin plane [^{1}H-NMR (360 MHz, CD_2Cl_2): $\delta = -2.79$ (s, 2H, NH), 0.09-0.14 ('dd', 8H, δ-CH_2), 0.40-0.47 (m, 8H, γ-CH_2), 0.78-0.84 (m, 8H, β-CH_2), 1.97 (s, 12H, OCH_3), 2.07-2.09 ('dd', 8H, α-CH_2), 4.31 (s, 4H, dimethoxy-subst. rings), 7.52-7.54 ('d', $J = 7.5$ Hz, 4H, 3-H), 7.57-7.61 ('dd', $J \approx 7.4$ Hz, 4H, 5-H), 7.67-7.71 ('dd', $J \approx 7.4$ Hz, 4H, 4-H), 8.18-8.20 ('d', $J \approx 7.3$ Hz, 4H, 6-H), 8.55 (s, 8H, β-pyrrole-H)]. From these data the following points can be made: The eight β-pyrrole protons exhibit only one singlet; methylene protons which correspond to each other on the four bridges are equivalent, and compared to the respective protons in **2** are increasingly shielded by the porphyrin anisotropy in going from the periphery to the aromatic rings above and below the porphyrin center; the four aromatic protons of these two rings are equivalent and give rise to a singlet at $\delta = 4.31$ which is shifted upfield $\Delta\delta = 2.33$ relative to **2**; the four methoxy groups are also equivalent and their singlet at $\delta = 1.97$ shows an upfield shift $\Delta\delta = 1.79$ ppm relative to **2**. These data very strongly indicate the highly symmetrical structure **5** with the two aromatic rings arranged parallel to the porphyrin plane (cf. the ^{1}H-NMR data for compound C[7]).



5

Demethylation of **5** under mild conditions (BBr_3, dichloromethane, 3 h, −40°C, exclusion of light) and subsequent oxidation with 1,2-dichloro-4,5-dicyano-*p*-benzoquinone (DDQ) [dichloromethane/methanol (1 : 1), 1 h, 20°C] yielded the bisquinone **1** in 41% yield after chromatography (neutral alumina Brockmann 2–3, toluene) and crystallization from toluene/hexane.

1 forms violet needles of m.p. = 281–282°C[4]. In the mass spectrum the molecular ion $m/z = 1046$ forms the base peak; compared to **5**, however, there is much more pronounced fragmentation which is clearly due to the lability of the quinone rings. The ^{1}H-NMR spectrum closely resembles that of **5** and, thus, strongly supports the arguments put forward for the spatial structure of these systems [^{1}H-NMR (360 MHz, CD_2Cl_2): $\delta = -2.82$ (s, 2H, NH), 0.13-0.16 ('dd', 8H, δ-CH_2), 0.28-0.30 (m, 8H, γ-CH_2), 0.84-0.86 (m, 8H, β-CH_2), 2.29-2.31 ('dd', 8H, α-CH_2), 4.04 (s, 4H, quinone-H), 7.54-7.56 ('d', $J \approx 6.8$ Hz, 4H, 3-H), 7.61-7.64 ('dd', $J = 6.8$ Hz, 4H, 5-H), 7.68-7.70 ('dd', $J \approx 6.8$ Hz, 4H, 4-H), 8.41-8.43 ('d', $J \approx 6.3$ Hz, 4H, 6-H), 8.64 (s, 8H, β-pyrrole-H)].

Conversion of **1** into metalloporphyrins and the study of electron-transfer reactions, which because of the specific structure of the doubly quinone-shielded **1** must involve quinone-porphyrin interactions, are presently being investigated by optical and EPR spectroscopy.

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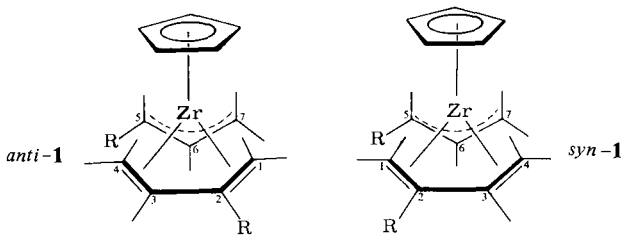
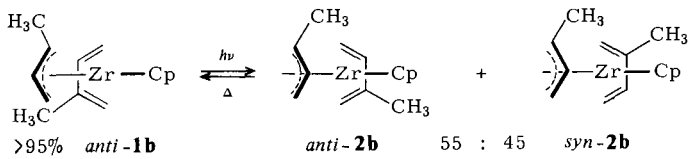
[7] Compound C: violet microcrystals, m.p. = 296–297 °C (from dichloromethane/methanol; MS: *m/z* 1106 ($M^{\oplus}$, 100%), 1092 (2), 1078 (7), 553 ($M^{\oplus}/2$, 30); ^{1}H-NMR (360 MHz, CD_2Cl_2); $\delta = -2.81$ (s, 2H), 0.78-1.44 (m, 14H), 1.73-1.89 (m, 4H), 2.25 (s, 3H), 2.29 (s, 3H), 2.40-2.52 (m, 2H), 2.56-2.73 (m, 10H), 2.75-2.85 (m, 2H), 3.67 (s, 6H), 5.40 (s, 1H), 5.43 (s, 1H), 6.23 (s, 2H), 7.39-7.48 ('dd', $J \approx 7.5$ Hz, 4H), 7.68-7.80 (m, 12H), 8.46 (s, 4H), 8.49 (s, 4H).

Diastereoselective Formation of Substituted (η^3-Allyl)(η^4-diene)ZrCp Complexes by Intramolecular Ligand Interaction**

By *Gerhard Erker**, *Klaus Berg*, *Reinhard Benn*, and *Gerhard Schroth*

Most of the catalysts in use today have been developed empirically. However, there has been no lack of attempts to synthesize homogeneous catalysts according to plan[1]. A basic problem in directed syntheses is the control of selectivity. A prerequisite for a specific product formation at the metal center is a pronounced intramolecular interaction between different ligands[2]. We have recently synthesized the isomeric (η^3-allyl)(η^4-diene)ZrCp complexes **1** and **2**[3], which, because of the different arrangement of the three π-ligands, can be expected to exhibit different intramolecular ligand interactions.

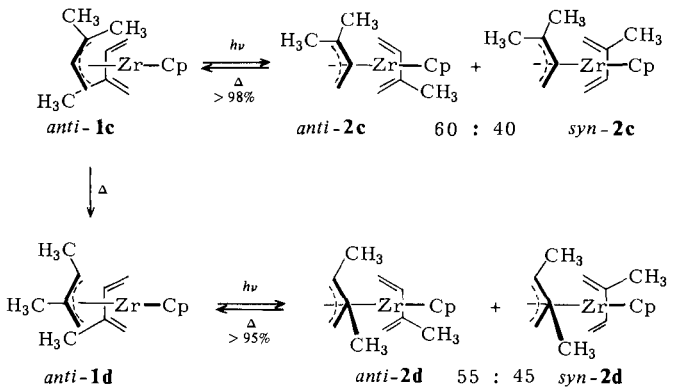




Scheme 1.

In the thermodynamically more stable isomer **1** the η^3-allyl and η^4-diene moieties open towards the apical cyclopentadienyl (Cp) ligand. According to an X-ray structure analysis and the ^{1}H-NMR-NOE difference spectra of the parent system[3] (η^3-allyl)(η^4-butadiene)(η^5-cyclopentadienyl)zirconium **1a**, the hydrogen atoms at C-2 of the diene and in the *syn*-position at C-5 of the allyl ligand come spatially very close (see Scheme 1); with respect to the C-2, C-5 vector they are almost eclipsed. The introduction of substituents at these positions leads to the formation of diastereomers. A strong repulsive interaction between these ligands should result in a preferential occurrence of *anti*-**1** over *syn*-**1** under equilibrium conditions. We could demonstrate this effect by introduction of methyl groups at the 2- and 5-positions to give the (η^4-isoprene)(η^3-1-methylallyl)ZrCp system **1b/2b**.

1b/2b was synthesized via the route previously described by us for **1a/2a**[3,4]: $CpZrCl_3$ **3**[5] is allowed to react with 2-butenylmagnesium chloride **4**; subsequent comproportionation with two equivalents of the starting material and reaction with "isoprene-magnesium" **7**[6] gives **1b/2b** in ca. 10% total yield as a red solid which is very sensitive to air and moisture. The material isolated at room temperature is photolyzed (Philips HPK 125, Pyrex filter) in toluene (≈5% solution) at −50 °C; the compounds *syn*-**2b** and *anti*-**2b** are obtained in a 45:55 ratio (^{1}H-NMR). Both



Scheme 2.

isomers rearrange on heating—within the range of accuracy of the measurement (^{1}H-NMR) at equal rates ($\Delta G^{\ddagger}_{10\,°C} = 21.7 \pm 0.3$ kcal/mol)—to give essentially one product (diastereoselectivity >95%), which according to the NMR analysis is the expected isomer *anti*-**1b**[7,8].

This effect is not limited to the system **1b/2b**. The (1,1-dimethylallyl)(isoprene)ZrCp system **1c/2c** as well as (1,2-dimethylallyl)(isoprene)ZrCp **1d/2d**, readily available therefrom by a thermally induced hydrogen-shift, behave analogously[9]. The formation of the photoisomers **2c** and **2d**, in which the allyl and diene moieties open towards the basis of the skeletal framework, is unselective. The thermal rearrangement affords only the thermodynamically more stable diastereomers *anti*-**1c** and *anti*-**1d**, respectively.

Therefore, it seems promising to us to attempt the development of catalyst systems for stereoselective syntheses using the chiral building blocks (η^3-1-methylallyl)ZrCp, (η^4-isoprene)ZrCp[3b] or metal-complex fragments of similar structure[11].

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[+] NMR spectroscopic investigations.

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[7] ^{1}H-NMR (400 MHz, [D$_8$]toluene, δ values, rel. TMS): *anti*-**1b** (300 K): Cp: 6.12; isoprene: −0.83 (*anti*-1-H), 2.02 (*syn*-1-H), 1.87 (s, C-2-CH$_3$); 5.39 (3-H), −0.47 (*anti*-4-H), 1.58 (*syn*-4-H); allyl: 2.16 (*anti*-5-H), 1.43 (d, 5, 8 Hz, C-5-CH$_3$), 5.76 (6-H), 0.89 (*anti*-7-H). Selected coupling constants [Hz]: J(*syn*-1-H, *anti*-1-H), J(*syn*-4-H, *anti*-4-H) = 7.5, J(*anti*-5-H,6-H) = 14.1, J(6-H, *anti*-7-H) = 13.2, J(6-H, *syn*-7-H) = 9.4.—*anti*-**2b** (223 K, same sequence): Cp: 4.76; isoprene; −1.84, 3.60, 1.89 (CH$_3$), 4.96, −0.88, 3.03; allyl: 1.36, 1.94 (CH$_3$), 5.84, 1.21, 2.88.—*syn*-**2b** (223 K): Cp: 4.75; isoprene: −1.55, 3.28, 1.96 (CH$_3$), 4.96, −1.29, 3.46; allyl: 1.89, 2.01 (CH$_3$), 5.80, 0.70, 2.90. The positional data *syn* and *anti* for the H atoms in positions 1/4 and 5/7 are with respect to the H atoms 2/3 and 6, respectively.
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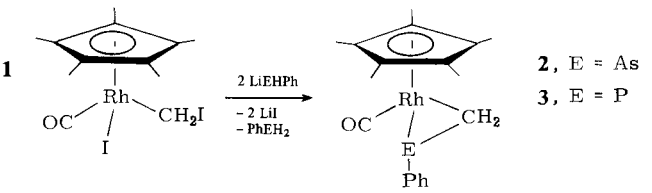
[10] ^{1}H-NMR (400 MHz), [D$_8$]toluene, δ values, rel. TMS, for sequence see [7]): *anti*-**1c** (300 K): Cp: 6.02; isoprene: −0.84, 1.89, 1.86 (CH$_3$), 5.49, −0.15, 1.85; allyl 1.02 (*anti*-C-5-CH$_3$), 1.67 (*syn*-C-5-CH$_3$), 5.56, 1.25, 1.00.—*anti*-**1d** (300 K): Cp: 6.00; isoprene: −0.87, 2.14, 1.82 (CH$_3$), 5.06, 0.09, 1.79; allyl: 2.05, 1.42 (d, 5.7 Hz, *syn*-C-5-CH$_3$), 1.96 (C-6-CH$_3$), 1.14, 1.18.
[11] A similar control of diastereomer formation has been described for an analogously structured bis(η^4-isoprene)(phosphane)iron(0) system: S. D. Ittel, F. A. Van-Catledge, J. P. Jesson, *J. Am. Chem. Soc. 101* (1979) 3874.

Complexation of PhAs=CH$_2$ and Synthesis of a Novel RhAs$_3$-Metallaheterocycle**

By *Helmut Werner**, *Wilfried Paul*, and *Ralf Zolk*

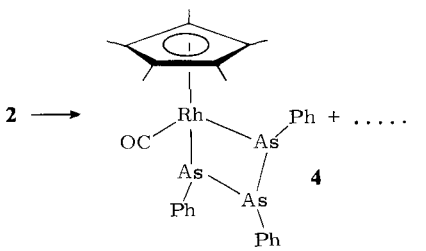
So far only one methylenephosphane RP=CH$_2$, the extremely reactive compound with R = 2,4,6-*t*Bu$_3$C$_6$H$_2$, is known[1a]. Analogous compounds R−E=CR$'_2$ with R$'$ = *t*Bu or OSiMe$_3$ were first prepared and structurally characterized by *Becker* et al.[1b], and subsequently also by other groups[1c]. With regard to their stability, particularly for methylenearsanes R−As=CR$'_2$, it appears that an almost complete shielding of the polar As=C bond by bulky groups R is of great importance. Convincing support for this statement comes from the work of *Bickelhaupt* et al.[2], who observed a striking difference in reactivity between (2,4,6-Me$_3$C$_6$H$_2$)As=CPh$_2$, which is stable at room temperature, and Ph−As=CPh$_2$, which immediately polymerizes under the same conditions.

Following the same method of synthesis which recently enabled us to prepare thio-, seleno- and telluroformaldehyde complexes of cobalt and rhodium[3], we have now succeeded in generating and stabilizing Ph−As=CH$_2$, a compound unknown in the free state, in the coordination sphere of a transition metal. The synthesis makes use of complex **1**, formed from C$_5$Me$_5$Rh(CO)$_2$ and CH$_2$I$_2$[3c]. **1** reacts with LiAsHPh[4a] in Et$_2$O/tetrahydrofuran at room temperature to produce **2**[5a]. Evidence for the proposed structure with an η^2-coordination of the methylenearsane via As *and* C emerges from the ^{1}H-NMR spectrum[5b], in which two well separated signals for the CH$_2$-protons are observed, as in C$_5$Me$_5$Rh(η^2-CH$_2$Se)CO[3c].



Reaction of **1** with LiPHPh[4b] follows a similar course. Compound **3** has not as yet been characterized analytically, but on basis of the spectroscopic data there is no doubt about its composition and structure. *Bickelhaupt* et al.[6a, b] as well as *Nixon* et al.[6c, d] have prepared complexes of Cr, Mo, W, Rh, and Pt with (2,4,6-Me$_3$C$_6$H$_2$)P=CPh$_2$ as ligand; spectroscopic measurements and X-ray analysis showed in nearly all cases that the diphenylmethylenephosphane molecule is linked *only via phosphorus* to the metal. Evidence for coordination via P *and* C has been found only in the platinum(0) complex [(2,4,6-Me$_3$C$_6$H$_2$)P=CPh$_2$]Pt(Ph$_2$PCH$_2$)$_3$CMe[6e] and in the nickel complexes [(2,6-Me$_2$C$_6$H$_3$)P=CPh$_2$]Ni(bpy)[6f] and [(Me$_3$Si)$_2$HCP=C(SiMe$_3$)$_2$]Ni(PMe$_3$)$_2$[6g], in which, as in **3**, an electron-rich metal is present.

Attempts to obtain single crystals of **2** from pentane led to a yellow microcrystalline powder (**2** according to mass spectroscopy) as well as to some orange-red crystals **4**, which are formed from **2**[5b]. At present, no detailed mechanism for the formation of **4** can be formulated. The X-ray structure analysis (Fig. 1)[7] shows the presence of a nonplanar, four-membered RhAs$_3$-ring in which the angle between the planes Rh, As1, As2 and Rh, As3, As2 is 25.9° and that between the planes Rh, As1, As3 and As1, As2, As3 is 23.1°. The As−As distances correspond to single bonds and are only slightly different from those in *cyclo*-(AsCF$_3$)$_4$ (245.4(1) pm)[8a] and *cyclo*-(AsPh$_6$) (average distance 245.9 pm)[8b]. The angle As1-As2-As3 (82.97(5)°) is also similar to that in *cyclo*-(AsCF$_3$)$_4$ (83.6(1)°).



4 is the second example of a heterocycle derived from a *cyclo*-(AsR)$_4$ ring system in which one AsR unit is replaced by a transition metal moiety (C$_5$Me$_5$(CO)Rh). The first example was described by *Köpf* and *Görges*, who isolated the complex (C$_5$H$_5$)$_2$Ti(AsEt)$_3$[9]. More recently, *Shaver* et al. reported the synthesis and crystal structure of the compound (C$_5$Me$_5$)$_2$TiS$_3$, which also contains a four-membered ring (though somewhat more bent than in **4**) formed from one transition-metal and three non-metallic atoms[10].

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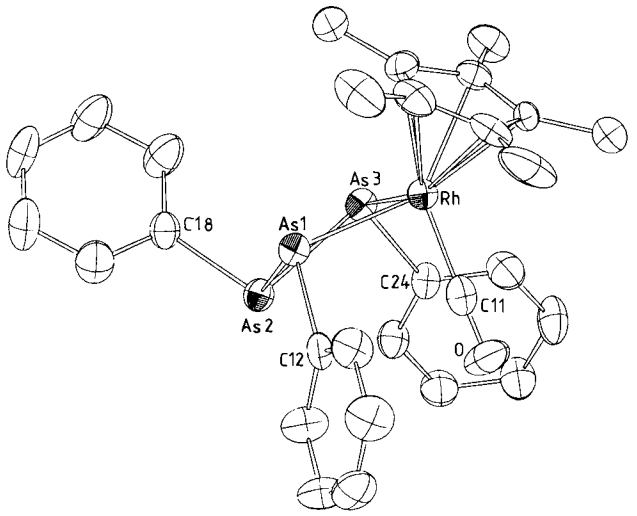

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Chemical Bonds without Bonding Electron Density—Does the Difference Electron-Density Analysis Suffice for a Description of the Chemical Bond?**

By *Dieter Cremer** and *Elfi Kraka*

Carefully executed X-ray diffraction experiments on peroxides[1,2] have indicated that the difference electron-density distribution $\Delta\rho(r)$ in the region of the OO bond is negative. The $\Delta\rho(r)$-distributions in certain CC, CN, CO, and CF bonds in various organic molecules are also surprisingly small[2,3]. Since $\Delta\rho(r)$ provides at least a qualitative measure for the accumulation of electron density in the bonding region[4], bonding models in which the existence of a covalent bond is dependent upon a finite bonding electron density $\Delta\rho(r)$ appear somewhat dubious[2]. We report here a novel approach to the description of the chemical bond, which confirms that the formation of covalent bonds does not necessarily bring about an increase in electron density in the bonding region.

The analysis of difference or deformation electron-densities $\Delta\rho(r) = \rho(r) - \rho'(r)$, although experimentally quite useful, is problematic since it requires the definition of an appropriate reference density $\rho'(r)$[4,5]. Therefore, we have analyzed the electron-density distribution $\rho(r)$ directly from its assigned Laplace field $\nabla^2\rho(r)$. It is an important property of the Laplace field to indicate concentrations of its associated scalar field without requiring a reference field[6]. The "Laplace concentration" reflects the behavior of the principle curvatures λ_i (i = 1, 2, 3) of $\rho(r)$ in the three directions of space (λ_i: eigenvalue of the matrix of second derivatives of $\rho(r)$). The curvature λ_1 along the bond is always positive since $\rho(r)$ has a minimum there. The curvatures λ_2 and λ_3 perpendicular to the bond axis are negative, corresponding to an increase in $\rho(r)$ towards the bond axis. If the charge concentration perpendicular to the bond axis is predominant ($|\lambda_2| + |\lambda_3| > |\lambda_1|$), a negative value for $\nabla^2\rho(r)$ results, synonymous with a concentration of $\rho(r)$ in the bonding region.

The Laplace fields $\nabla^2\rho(r)$ determined by HF/6-31G* calculations for some selected bonds are shown in Figure 1 in the form of contour line diagrams. The broken lines occur in regions with charge concentrations ($\nabla^2\rho(r) < 0$) which, on the basis of simple chemical concepts, can be assigned to bonding and lone-pair electrons[7]. The concentration of $\rho(r)$ in the bonding region decreases along the series CC, CN, CO, CF and CC, OO, FF, respectively (see Fig. 1 and Table 1), which qualitatively goes hand in hand with a decrease in covalent bond strength[8].

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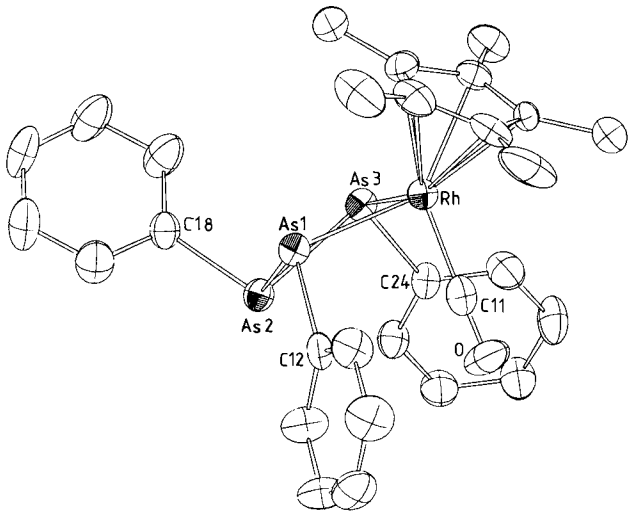

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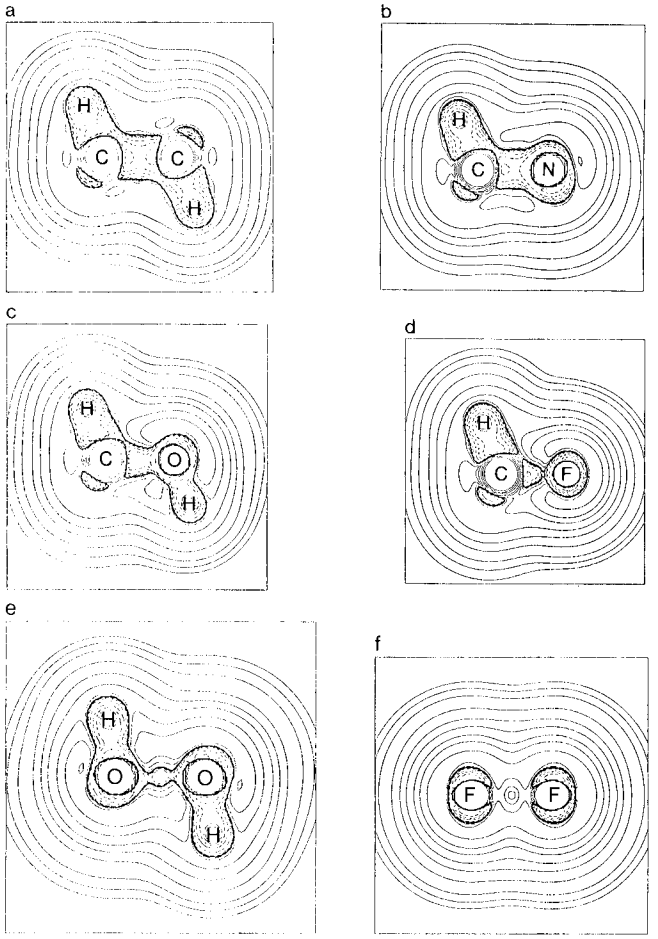

Fig. 1. Contour line diagram of the Laplace field $\nabla^2\rho(r)$ (HF/6-31G* calculations) for a) C_2H_6 (staggered), b) CH_3NH_2 (staggered, HCN *trans*), c) CH_3OH (staggered, HCOH *trans*), d) CH_3F, e) H_2O_2 (trans), and f) F_2. Broken lines indicate regions with charge concentrations. Atoms lying outside the reference plane are not shown.

In contrast to the results of the analysis of $\Delta\rho(r)$[1], the Laplace field of $\rho(r)$ indicates that charge is concentrated in the region of the OO bond. Apparently, the quantity $\nabla^2\rho(r)$ is a more sensitive measure for the description of charge accumulation than $\Delta\rho(r)$. The experimental observation that bonding electron density can be absent for specific covalent bonds is, however, confirmed in the case of the FF bond[9]. Clearly, a characterization of the covalent bond by $\nabla^2\rho(r)$ is insufficient. The chemical bond can only be satisfactorily described if in addition to electrostatic also energetic aspects are considered[10].

Bond formation is associated with a gain in molecular energy, and this gain is a result of a complex interplay of changes in potential and kinetic energy[11]. One possibility to analyze these changes in the bonding region is provided by the relation $2G(r)+V(r)=\frac{1}{2}\nabla^2\rho(r)$, derived by *Bader*, which connects the kinetic energy density $G(r)$ and the potential energy density $V(r)$ with the Laplace field of $\rho(r)$[12]. Pointwise analysis of $G(r)$ and $V(r)$ indicates that for covalent bonds the local energy density $H(r)=G(r)+V(r)$ at sites of maximum concentration of $\rho(r)$ is always negative (stabilizing)[12b, 13]. This also applies to the F–F bond: Although electron density flows out of the internuclear region upon bond formation, the residual density is sufficient to contribute towards bond stabilization via an increase in $|V(r)|$ (Table 1).

Table 1. Characterization of covalent bonds by electron density and energy density [a].

Molecule	Bond	$\rho(r_C)$ [e·Å^{-3}]	$\nabla^2\rho(r_C)$ [e·Å^{-5}]	$G(r_C)$	$V(r_C)$ [Hartree·Å^{-3}]	$H(r_C)$
C_2H_6	C–C	1.880	−24.844	1.032	−3.803	−2.771
CH_3NH_2	C–N	1.866	−22.713	0.935	−3.466	−2.531
CH_3OH	C–O	1.858	−18.366	0.983	−3.267	−2.284
CH_3F	C–F	1.769	−10.517	1.199	−3.134	−1.935
H_2O_2	O–O	1.837	−4.753	1.190	−2.713	−1.523
F_2	F–F	2.335	2.908	2.247	−4.292	−2.045

[a] HG/6-31G* calculations with optimized geometries. The point r_C corresponds to the maximum density in the bonding region.

The condition $H(r)<0$ in the bonding region holds for all covalent bonds studied to date (ca. 100)[13]; not, however, for ionic bonds, H bonds, or van der Waals bonds. Thus, specifically those bonds which exhibit either zero or a very small bonding electron density should be investigated with the aid of the local energy density $H(r)$. For this purpose, analysis of the local property $H(r_c)$ is adequate for a qualitative description of bonding, whereas for a quantitative treatment the behavior of $H(r)$ in the whole bonding region must be considered[13].

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[5] Difficulties arise, inter alia, in the investigation of ions with delocalized charge, e.g. cations or anions of cyclopolyenes.
[6] The significance of the Laplace field can be understood from the definition of the second derivative. In the one-dimensional case

$$\lim_{\Delta x\to 0}\{\rho(x)-\tfrac{1}{2}[\rho(x-\Delta x)+\rho(x+\Delta x)]\}=$$
$$-\tfrac{1}{2}\lim_{\Delta x\to 0}\{[\rho(x+\Delta x)-\rho(x)]-[\rho(x)-\rho(x-\Delta x)]\}=-\tfrac{1}{2}(\rho/\mathrm{d}x^2)\cdot\mathrm{d}x^2$$

is valid.
If the second derivative, and hence the curvature of ρ, is negative, $\rho(x)$ is larger than the average value of ρ at all neighboring points; P. M. Morse, H. Feshbach: *Methods of Theoretical Physics, Bd. 1*, McGraw-Hill, New York 1953, p. 6.
[7] R. F. W. Bader, *J. Am. Chem. Soc.*, in press.
[8] A significant correlation between electron density properties and thermochemically derived bond energies is obtained if the total electron density in the bonding region is considered. See e.g. R. F. W. Bader, T. Tang, Y. Tal, F. W. Bieler-König, *J. Am. Chem. Soc. 104* (1982) 946.
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[10] According to the Hohenberg-Kohn theorem (P. Hohenberg, W. Kohn, *Phys. Rev. 136* (1964) B864) an as yet unknown connection exists between energy and electron density.
[11] K. Ruedenberg, *Rev. Mod. Phys. 34* (1962) 326.
[12] a) R. F. W. Bader, *J. Chem. Phys. 73* (1980) 2871; b) $G(r)$ and $V(r)$ are defined by the first-order density matrix $\Gamma^1(r,r')$:

$$G(r)=\tfrac{1}{2}\nabla\nabla'\Gamma^1(r,r')|_{r=r'};\ V(r)=\mathrm{trace}\ \ddot{\sigma}(r),$$
$$\ddot{\sigma}(r)=\tfrac{1}{4}[(\nabla\nabla+\nabla'\nabla')-(\nabla\nabla'+\nabla'\nabla)]\Gamma^1(r,r')|_{r=r'}$$

When integrated over the total molecular space, $G(r)$ and $V(r)$ yield the kinetic and potential energies of the molecule, respectively. Correspondingly, $E=\int H(r)\,\mathrm{d}r$ applies for the electronic molecular energy.
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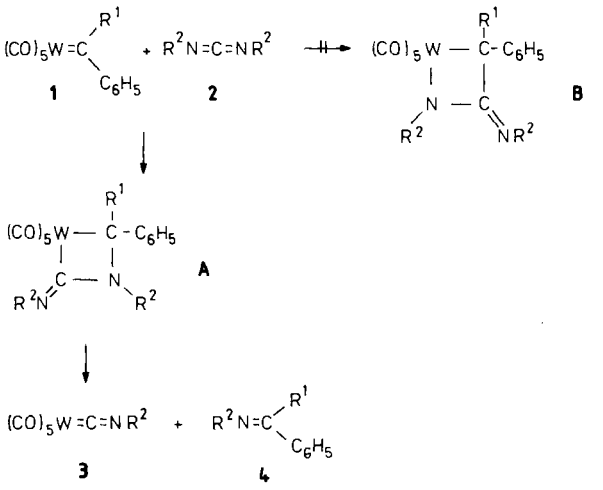
Stoichiometric and Catalytic Metathesis of Carbodiimides and Pentacarbonylcarbenetungsten Complexes**

By *Karin Weiss** and *Petra Kindl*

The carbene complexes pentacarbonyl(diphenylcarbene)tungsten **1a**[1] and pentacarbonyl[methoxy(phenyl)carbene]tungsten **1b**[2] exhibit low activity as metathesis catalysts and so are especially suitable for the investigation of stoichiometric model reactions such as, e.g., metathesis with alkenes or vinyl ethers[2,3]. Stoichiometric or catalytic metathesis reactions have so far been achieved with cyclic or acyclic alkenes, which only in exceptional cases contained substituents bearing heteroatoms. Metathesis reactions of heteroallenes with carbene complexes were hitherto unknown. Isocyanates react as heteroallenes with carbonyl compounds as catalysts to give carbodiimides and CO_2[4], a metathesis which has so far not been recognized as such. On reaction of the model catalysts **1** with the heteroallenes dicyclohexylcarbodiimide **2a** and diisopropylcarbodiimide **2b**, we obtained the metathesis products pentacarbonyl(cyclohexylisocyanide)tungsten **3a** or pentacarbonyl(isopropylisocyanide)tungsten **3b**, as well as the Schiff bases *N*-(diphenylmethylene)cyclohexylamine **4a**, *N*-(diphenylmethylene)isopropylamine **4b** and *N*-(α-methoxybenzylidene)isopropylamine **4c**. The reactions (in pentane at 20 °C) were monitored spectroscopically (IR: ν-N=C=N–). Reaction of complex **1a** was complete after 3 h, whereas **1b** was completely converted only after 24 h[5].

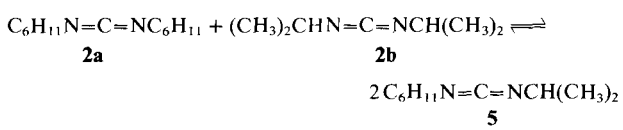


Reaction	R^1 (from **1**)	R^2 (from **2**)	Yield [%] **3**	**4**
1a + **2a** → **3a** + **4a**	Ph	*c*-Hex	98	95
1a + **2b** → **3b** + **4b**	Ph	*i*Pr	88	93
1b + **2b** → **3b** + **4c**	OMe	*i*Pr	79	90

The course of the metathesis can be easily explained in terms of an azatungstacyclobutane intermediate. Similar metallacyclobutane intermediates are postulated for metathesis reactions of alkenes[6]. Two different orientations of the carbodiimides with respect to the W=C(carbene) bond are conceivable (A and B). From the reaction products it follows that there is a clear selectivity for orientation A; a pentacarbonyl(imido)tungsten should be formed from B (cf. [7]).

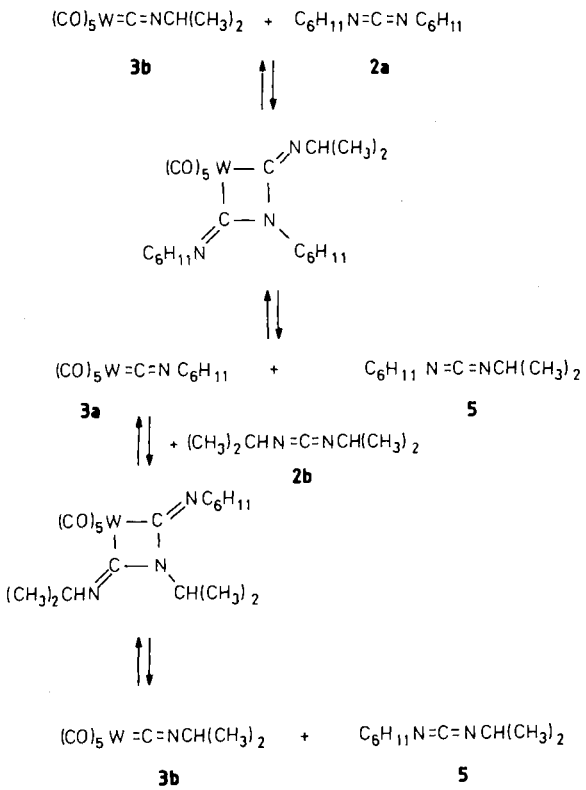
In metathesis reactions with carbene complexes of the Fischer-type, cyclopropanes are often also formed in a competing reaction by formal [2+1]-cycloaddition of the olefins with the carbene ligands[6]. However, in the reaction of the carbodiimides **2** with the carbene complexes **1** cycloadducts were not observed, only the products resulting from metathesis.

At 20 °C, the carbene complexes **1** are not active as catalysts for the metathesis of symmetrical carbodiimides, e.g. **2a** and **2b**.



Rather, the isocyanide complexes **3** and the Schiff bases **4** are formed stoichiometrically. The carbene complexes **1** and **2** catalyze the metathesis of **2a** and **2b** at temperatures greater than or 140 °C to give "mixed" carbodiimides **5**. That is, the isocyanide complexes **3**, formed in the course of the reaction from **1** and **2**, are thought to be the actual catalysts for the carbodiimide metathesis (2nd generation catalysts). Indeed, under these conditions (i.e. at 140 °C) **3a** and **3b** show the same catalytic activity as the carbene complexes **1**.

Since **1** and **3** catalyze both the forward as well as the reverse reaction, the conversion proceeds only until equilibrium is established, as in the case of the metathesis of acyclic olefins[8,9].



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[**] Investigations of Polymerization and Metathesis Reactions Part 2.— Part 1: K. Weiss, K. Hoffmann, *J. Mol. Catal.*, in press.

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The course of the reaction can be readily explained in terms of an (not detected) azatungstacyclobutane intermediate. With the exception of the formation and decomposition of the intermediates, the partial reactions can also be monitored stepwise. If, e.g., **3b** is allowed to react at 140 °C with excess dicyclohexylcarbodiimide **2a**, then **3a** as well as **3b** can be detected in the reaction mixture by mass spectrometry. Correspondingly, **3a** reacts with excess diisopropylcarbodiimide **2b** to give **3b**. These findings support the postulated reaction course as proceeding via isocyanide complexes, which are newly formed in each reaction step. The metathesis of two symmetrical carbodiimides to give "mixed carbodiimides" such as **5** with pentacarbonyl(isocyanide)tungsten complexes **3** as catalysts provides a facile route to these compounds, which can be used for numerous organic syntheses[10].

This first *catalytic* metathesis of carbodiimides shows that not only alkenes and alkynes undergo metathesis reactions, but that heteroallenes are also capable of doing so in the presence of suitable catalysts.

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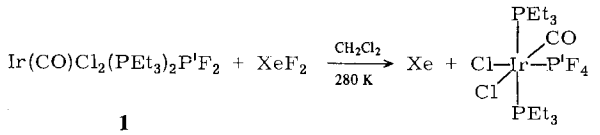
An Iridium(III) Complex Containing a PF_4-Group Bound to the Metal

By *E. A. V. Ebsworth*, John H. Holloway, Nicholas J. Pilkington,* and *David W. H. Rankin*

Compounds containing metal atoms bound to pentacoordinated P, As, or Sb atoms are rare[1-3]. We recently[3] described the complex $Ir(CO)Cl_2(PEt_3)_2(P'Cl_4)$ and characterized it by NMR spectroscopy and elemental analysis; however, the characterization of P' as pentacoordinated was based on the failure of solutions to conduct. By treating **1** with XeF_2, a valuable, mild, fluorinating agent[4], we have now synthesized $Ir(CO)Cl_2(PEt_3)_2(P'F_4)$, whose ^{19}F- and ^{31}P-NMR spectra unequivocally show the presence of the Ir–P'F_4 group.



1 **2**

The reaction is very slow at 220 K but rapid at or above 280 K. The product, which appears to be stable at room temperature in the absence of air or moisture, has been isolated as a white solid and characterized by partial elemental analysis and by NMR spectroscopy. The ^{31}P{^{1}H}-NMR spectrum in CD_2Cl_2 at 300 K consists of a broad quintet of triplets due to the P' nucleus (see Fig. 1a) and a narrow

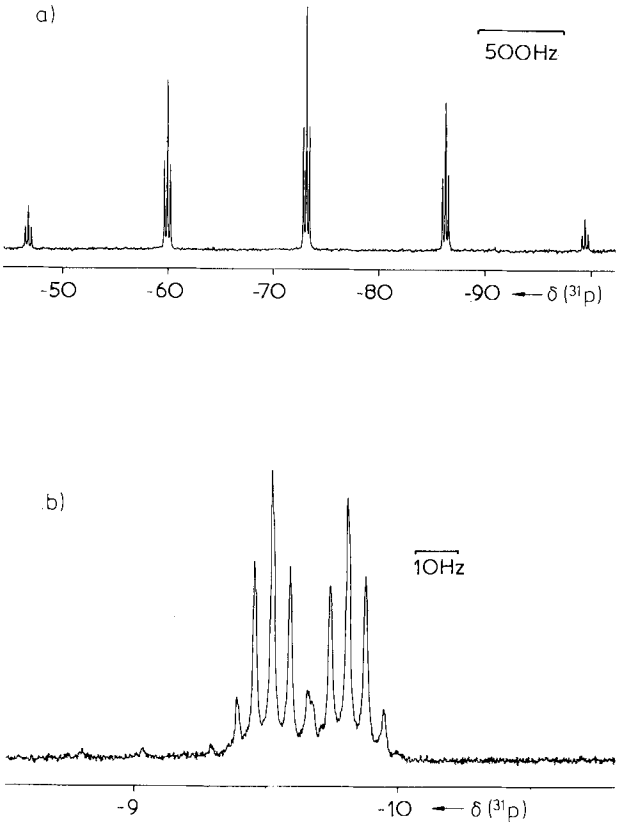


Fig. 1. Part of the 80.1 MHz ^{31}P{^{1}H}-NMR spectrum of **2** at 300 K in CD_2Cl_2; a) is assigned to the P' nucleus and b) to the P nuclei.

doublet of quintets due to the *P* nuclei (see Fig. 1b); the ^{19}F-NMR spectrum at 220 K in the same solvent is a broad doublet of triplets. The ^{31}P{^{19}F}-NMR spectrum is sharp at 220 K, but becomes very broad at 190 K, showing that the molecule is fluxional and that there must be at least two different F sites in the static structure.

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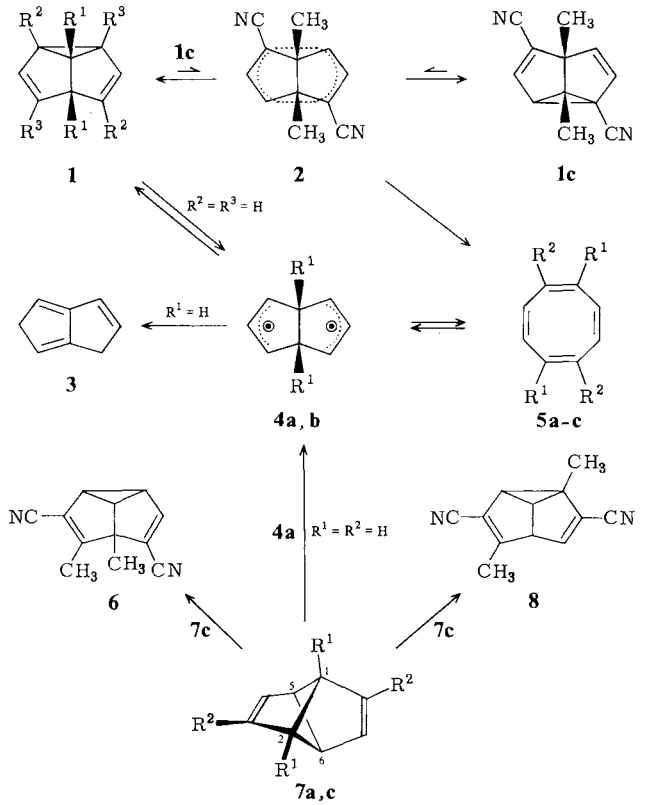
Temperature Dependence of the UV Spectrum of 1,5-Dimethyl-2,6-semibullvalenedicarbonitrile; Evidence for an Equilibrium with a Delocalized, Homoaromatic Isomer**

By *Helmut Quast** and *Josef Christ*

In our search for delocalized bishomoaromatic systems of the Dewar-Hoffmann type[1], we have now found, for the first time, experimental evidence for the existence of a semibullvalene of this type; we report here on the surprising temperature dependence of the UV spectrum of the 2,6-semibullvalenedicarbonitrile **1c**[1b,c,2], which suggests an equilibrium with the isomer **2**, and on the thermal isomerization of **1c** to the cyclooctatetraene **5c**.



	R^1	R^2	R^3
1a,4a,5a,7a	H	H	H
1b,4b,5b	CH_3	H	H
1c,5c,7c	CH_3	CN	H
1d	CH_3	CO_2CH_3	CO_2CH_3
1e	H	CN	CN

The 2,6-semibullvalenedicarbonitrile **1c** has the lowest of all previously determined Cope activation barriers ($\Delta G^{\neq}_{115} = 13.0 \pm 0.5$ kJ mol^{-1}[1c]). It forms sublimable crystals which are pale lemon-yellow at room temperature and which completely decolorize reversibly on cooling to 180 K. The UV spectrum of **1c** in solution is temperature dependent in the same way between 180 and 370 K (Table 1, Fig. 1): In butyronitrile at 180 K, the absorption in the near UV of a sample carefully degassed at 10^{-5} torr has virtually disappeared, whereas on warming to 300 K a new band is formed as a markedly pronounced shoulder at 360 nm, which amplifies on further warming to 366 K. If the thermal expansion of the solvent is taken into consideration, two isosbestic points are found at 291 and 241 nm. The changes in the spectrum with temperature are completely reversible. The absorption at 360 nm also occurs in non-degassed solutions and on using other solvents (Table 1), and does not depend on the concentration between 10^{-2} and 10^{-4} M. Since no impurities were detectable by gas chromatography[3] they could be ruled out as the cause of the temperature-dependent occurrence of the long-wavelength band.

Cyclooctatetraenes are generally yellow; we therefore checked the possibility of a thermal isomerization of the 2,6-semibullvalenedicarbonitrile **1c** to a cyclooctatetraene. This isomerization was accomplished by vacuum pyrolysis of the parent compound, the semibullvalene **1a**, and some alkyl-substituted semibullvalenes, e.g. **1b**[4]. **1c** is indeed isomerized in a yield of 98% (capillary GC) in solution, but only at 130°C in a slow irreversible first order reaction (benzene, $k_{403} = 3.0 \times 10^{-5}$ s^{-1}, $t_{1/2} = 6.5$ h); the product is a *colorless* cyclooctatetraene which, according to its NMR spectra, has the structure **5c**[5]. Therefore, the phenomenon cannot be interpreted in terms of this isomerization either.

Table 1. UV data of 10^{-3} M solutions of the semibullvalenedicarbonitrile **1c** and the barbaralanedicarbonitrile **9**.

Cpd.	Solvent	T [K]	λ_{max} (logε) [nm]			λ_{min} (logε) [nm]
1a	Cyclohexane[a]	293	212(3.927)	245(3.809)	360(1.792)(sh)	232(3.751)
	Butyronitrile	293	211(3.922)	246(3.831)	360(1.807)(sh)	232(3.750)
		178[b]		247(3.848)	—	232(3.720)
		297[b]		245(3.831)	360(1.779)(sh)	232(3.753)
		366[b]		243(3.825)	360(2.127)(sh)	232(3.776)
	Acetonitrile	293	211(3.913)	246(3.824)	360(1.797)(sh)	232(3.741)
	Ethanol	293	211(3.920)	245(3.828)	360(1.837)(sh)	232(3.751)
9	Butyronitrile	293	201(4.087)	239(3.926)		222(3.717)

[a] 10 mL Solution contained 0.050 mL acetonitrile. [b] Sample degassed at 10^{-5} torr. The temperature dependence of the volume was taken into account by means of the density of butyronitrile (178, 0.886; 297, 0.7885; 366 K, 0.720 g cm^{-3}).

The reversible temperature-dependent appearance of a new long-wavelength band in the UV spectra of **1c** can best be explained in terms of an unstable, optically readily excitable species in equilibrium. This species occurs in significant amounts only at higher temperatures. Since **1c** does not absorb at 360 nm, the apparent extinction coefficients ε_1 and ε_2 measured at 360 nm and at the temperatures T_1 and T_2 are proportional to the concentrations of the unstable species. The energy difference ΔE between stable and unstable structure can therefore be calculated

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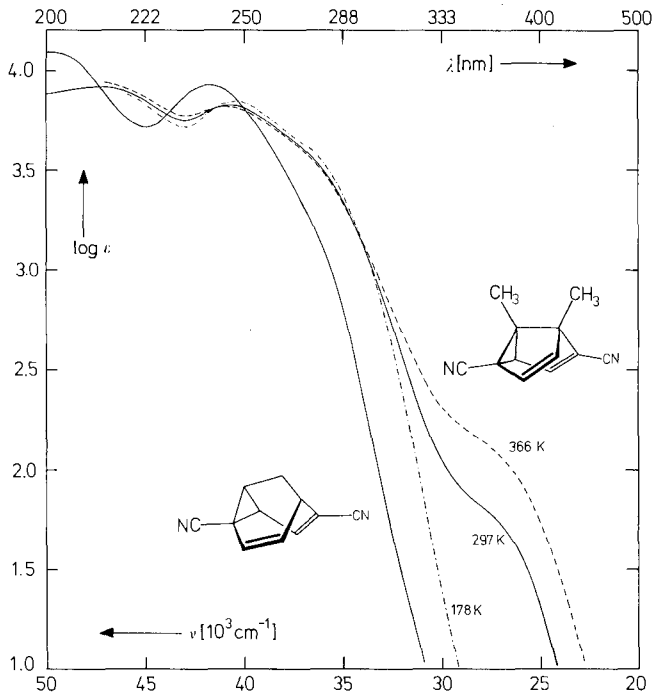

Fig. 1. UV spectra of the 2,6-semibullvalenedicarbonitrile **1c** (at 178, 297 and 366 K) and of the 2,6-barbaralanedicarbonitrile (**9**) (at 293 K) in butyronitrile.

on the basis of the Boltzmann distribution function[6] from the values in Table 1 according to $\varepsilon_1(1+\exp\Delta E/RT_1) = \varepsilon_2(1+\exp\Delta E/RT_2)$. This gives a value of 10.7 kJ mol^{-1}, which is ca. 2 kJ mol^{-1} smaller than the Cope activation barrier determined ^{13}C-NMR spectroscopically at 115 K[1c]. From the energy difference ΔE, equilibrium constants of $K_{178}=0.07\times10^{-2}$, $K_{297}=1.3\times10^{-2}$, and $K_{366}=2.9\times10^{-2}$ are obtained. Accordingly, only ca. 3% of the unstable species is present, even at 366 K. Its extinction coefficient in the near UV ($\varepsilon_{360}=4700$ L mol^{-1} cm^{-1}) corresponds to that of a $\pi^*\leftarrow\pi$ transition.

We propose that the unstable species isomeric to **1c** be assigned the *delocalized, bishomoaromatic* structure **2**. The UV spectroscopically detectable species **2** corresponds to a well-defined molecule in a shallow local minimum on the potential energy hypersurface, and *not* to the transition state of the Cope rearrangement of **1c**. Opening of the central bond C1–C5 of **2** at higher temperature leads to the cyclooctatetraene **5c**. Analogous intermediates **4** have been assumed for the thermal isomerizations **1a**→**5a**, **1b**→**5b**, **5a**→**3**[4], and **7a**→**1a**[7].

Because of the relatively long-wavelength absorption of the unstable semibullvalene isomer **7a** in the near UV[7b], structure **7c** must be considered as the unstable isomer of **1c**. As in **7a**[7c], the orthogonal π-systems of **7c** interact through the bonds of the cyclobutane ring. On the other hand, the tricyclo[3.3.0.0^{2,6}]octadiene structure, which is isomeric to **7c** but has the cyano groups attached to C5 and C6, lacks stabilization by conjugation between cyano groups and double bonds and, therefore, may be ruled out as a plausible alternative for **2**. However, the observation that the isomerization of the unstable isomer fails to produce the more stable[8] semibullvalenes **6** and **8**, besides **1c**, argues against the structure **7c**.

Consistent with the hypothetical existence of long-wavelength absorbing, unstable isomers in the case of semibullvalenes *with particularly low Cope activation barriers*, the crystals of the semibullvalenetetracarboxylate **1d** are brilliant yellow[9], whereas all other semibullvalenes, especially derivatives with electronegative substituents[10] and 2,6-barbaralanedicarbonitrile (**9**), do not absorb in the near UV. From the results obtained with **1c**, an analogous temperature dependence can be predicted for the UV spectrum of **1d**. Furthermore, it is remarkable in this connection that the most recent MNDO-CI calculations for the localized and the delocalized structure of the semibullvalenetetracarbonitrile **1e** indicate an energy barrier between both structures[8].

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[5] M.p. 150–151°C; UV (acetonitrile): $\lambda_{max}(\log\varepsilon)=215$ (4.375) (sh), 224 (4.401), 290 nm (2.749) (sh); ^{1}H-NMR ([D$_6$]benzene, 400 MHz): $\delta=1.490$ (2CH$_3$), 5.141 (3,7-H, H$_A$), 5.249 (4,8-H, H$_B$, $J_{AB}=11.3$ Hz); ^{13}C-NMR ($CDCl_3$, 100 MHz): $\delta=22.3$ (CH$_3$), 110.0 (C-1,5), 116.2 (CN), 128.2 (C-3,7), 135.3 (C-4,8), 155.3 (C-2,6). The yellow coloration which occurs on thermolysis in benzene remains on cooling and is due to small amounts of unknown byproducts.

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Novel Inorganic Ring Systems and Fixation of the $S_8^{2\ominus}$ Ion: $[(S_6)Cu(S_8)Cu(S_6)]^{4\ominus}$ and $[Cu_3(S_4)_3]^{3\ominus}$**

By *Achim Müller*, Friedrich-Wilhelm Baumann, Hartmut Bögge, Michael Römer, Erich Krickemeyer*, and *Klaus Schmitz*

The coordination behavior of polysulfide ions is unusually variable[1]. The reason for this is that they contain several coordination centers, each of which can coordinate differently. The analytical[2], biochemical[2], and geological[3] relevance of soluble polysulfido complexes and clus-

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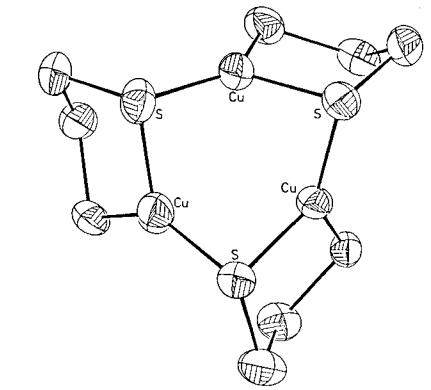
[**] Note added in proof: In the meantime, several compounds containing the $[AgS_9]^-$ ring system could be obtained too, for example, orange $(Ph_3P)_2N[AgS_9]\cdot S_8$ ($P\bar{1}$, $Z=2$, $a=1383.8(4)$, $b=1429.5(4)$, $c=1540.5(5)$ pm, $\alpha=62.38(2)$, $\beta=68.05(2)$, $\gamma=65.86(2)$) having a symmetrical $[AgS_9]^-$ ring (with approximate C_2 symmetry).

ters has already been outlined. In view of the large variety of Cu–S minerals, it had been presumed[4] that numerous polynuclear complexes and clusters exist in the $Cu^{n\oplus}/S_x^{2\ominus}$ system. We have so far synthesized salts of the anions $[Cu_3(S_6)_3]^{3\ominus}$[4], $[Cu_4(S_5)_3]^{2\ominus}$[2], $[Cu_4(S_5)_2(S_4)]^{2\ominus}$, $[Cu_4(S_5)(S_4)_2]^{2\ominus}$[2,3a], $[Cu_4(S_4)_3]^{2\ominus}$[5], and $[Cu_6(S_5)(S_4)_3]^{2\ominus}$[6]. Herein we report the synthesis and characterization of the polynuclear complex ions $[Cu_3(S_4)_3]^{3\ominus}$ **1** (Fig. 1, above) and $[(S_6)Cu(S_8)Cu(S_6)]^{4\ominus}$ **2** (Fig. 1, below).



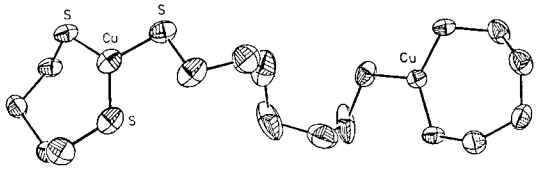


Fig. 1. Above: Structure of **1**. Bond lengths S–S 201.7(9)–212.4(8), Cu–S (in the Cu_3S_3 ring) 219.5(5)–229.8(6), Cu–S (outside of the Cu_3S_3 ring) 222.5(6)–224.1(6), Cu–Cu 295.0(3)–318.5(3) pm; bond angles (selected): S–Cu–S (CuS_4 ring) 105.5(2)–106.2(2), S–Cu–S (Cu_3S_3 ring) 116.3(2)–119.0(2), Cu–S–Cu 81.8(2)–90.6(2), Cu–S–S (in the CuS_4 ring) 98.9(3)–100.7(3), S–S–S 104.5(3)–105.6(4)°.—Below: Structure of **2**. Bond lengths: S–S (ring): 200.7(9)–208.9(9), S–S (chain) 197.0(12)–211.8(12), Cu–S 220.8(7)–226.1(6) pm; Bond angles (selected): S–Cu–S (ring) 130.9(3) and 128.1(2), S (ring)–Cu–S (chain) 112.9(3)–118.8(3), S–S–S (ring) 107.0(4)–111.9(4), S–S–S (chain) 103.9(5)–109.6(4)° [8].

The diamagnetic salts $[(C_6H_5)_4P]_2[NH_4][Cu_3(S_4)_3]\cdot 2CH_3OH$ **1a** (orange) (which can crystallize under slightly varying conditions, e.g. in the case of different H_2S flow rates, without solvent molecules (**1b**); for crystal data of **1b** see [7]) and $[(C_6H_5)_4P]_4[(S_6)Cu(S_8)Cu(S_6)]$ **2a** (reddish brown)[7] have been characterized by X-ray structure analysis and UV/VIS, IR, and Raman spectroscopy[9, 10]. **1** consists of three CuS_4 five-membered rings with half-chair conformation and a central Cu_3S_3 six-membered ring with alternating short and long Cu–S bond lengths and chair conformation (Fig. 1, above). In MS_4 ring systems one finds both the aforementioned half-chair conformation as well as the envelope conformation. The anionic complex has almost C_3 symmetry.

2 consists of two CuS_6 seven-membered rings with different conformations (having approximately C_2 and C_s symmetry, respectively) which are linked via an $S_8^{2\ominus}$ ligand. The Cu atoms are trigonal-planar coordinated. So far, neither a complex with an $S_8^{2\ominus}$ ligand nor a salt with an isolated $S_8^{2\ominus}$ ion has been reported in the literature[1]. A longer $S_x^{2\ominus}$ ligand has hitherto only been found in the anion $[AuS_9]^{\ominus}$[11].

The above-mentioned, previously synthesized trinuclear and tetranuclear clusters (the short Cu–Cu distances point to metal-metal interactions and justify the term cluster) with $S_4^{2\ominus}$ and $S_5^{2\ominus}$ ligands are orange or deep orange ($\lambda_{max} < 400$ nm), whereas **2a** is reddish-brown; this color can be ascribed to an internal ligand transition in the $S_8^{2\ominus}$ chain (shoulder at ca. 470 cm[9]).

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[1] Reviews on polysulfido complexes: M. Schmidt, G. Hoffmann, *Z. Naturforsch. B34* (1979) 451; A. Müller, E. Diemann, G. Wilkinson, J. A. McCleverty, R. J. Gillard: *Comprehensive Coordination Chemistry*, Pergamon Press, Oxford, in press, Vol. 1, Part 2, Chap. 16.1; A. Müller, W. Jaegermann, J. H. Enemark, *Coord. Chem. Rev. 46* (1982) 245.

[2] A. Müller, M. Römer, H. Bögge, E. Krickemeyer, K. Schmitz, *Inorg. Chim. Acta 85* (1984) L39.

[3] a) A. Müller, M. Römer, E. Krickemeyer, H. Bögge, *Naturwissenschaften 71* (1984) 43; b) A. Müller, J. Schimanski, U. Schimanski, *Angew. Chem. 96* (1984) 158; *Angew. Chem. Int. Ed. Engl. 23* (1984) 159.

[4] A. Müller, U. Schimanski, *Inorg. Chim. Acta 77* (1983) L187.

[5] The deep orange compound $[(C_6H_5)_4P]_2[Cu_4(S_4)_3]\cdot CH_3CN$ is formed in pure form on passing H_2S (0.5 min) into NH_3-saturated acetonitrile (100 mL) and treatment of this solution with a solution of 1 g $Cu(CH_3COO)_2\cdot H_2O$ in CH_3CN (50 mL) in the presence of oxygen and a trace of sulfur.

[6] A. Müller, M. Römer, H. Bögge, E. Krickemeyer, D. Bergmann, *J. Chem. Soc. Chem. Commun. 1984*, 348; G. Henkel, P. Betz, B. Krebs, *ibid. 1984*, 314.

[7] *Procedure:* **1a**: NH_3 was passed into a suspension of 1.0 g $Cu(CH_3COO)_2\cdot H_2O$ in 30 mL CH_3OH for 10 min (formation of a blue solution). After addition of 0.5 g sulfur and 0.5 g $[(C_6H_5)_4P]Br$, H_2S was passed into the reaction solution for 0.5 min (flow rate 6 L/h (precipitated copper sulfide was filtered off). The orange crystals of **1a** which precipitated from the filtrate after 2 d (closed vessel; 5°C) were washed with methanol and toluene and dried in air. Yield: 0.3 g.—**2a**: NH_3 was passed into 200 mL CH_3CN (analytically pure; dried) for 20 min. After addition of 5.0 g $[(C_6H_5)_4P]Br$ and 2.0 g sulfur, H_2S was passed for 2 min (6 L/h) into the vigorously stirred mixture (color change from blue through green to brown). The vigorously stirred reaction mixture was treated with a mixture of 2.0 g $Cu(CH_3COO)_2\cdot H_2O$, 4.0 g $[(C_2H_5)_4N]I$, and 50 mL (analytically pure) CH_3CN (which was stirred for 20 min), restirred for 0.5 min, and filtered. After 1-3 d (closed vessel; Ar atmosphere; 20-25°C) reddish brown **2a** and sulfur precipitated from the brown filtrate; the precipitate was filtered off and washed several times with toluene (alternatively with water, isopropanol and toluene). Yield: 1.8 g.
Under the experimental conditions quoted in [5], but after addition of 0.8 g sulfur, $[(C_6H_5)_4P]_2[NH_4][Cu_3(S_4)_3]$ **1b** precipitated out after 1d; crystallographic data: $P\bar{1}$, $Z=2$; $a=1266.0(5)$, $b=1489.6(6)$, $c=1493.6(6)$ pm, $\alpha=74.72(3)$, $\beta=86.40(3)$, $\gamma=77.52(3)°$, $V=2652.9\times10^6$ pm^3. After 4 d **2a** crystallized from the filtrate.

[8] X-ray structural analyses: **1a**: $P2_1/c$, $a=2317.4(7)$, $b=1458.4(4)$, $c=1843.1(5)$ pm, $\beta=108.68(2)°$, $V=5901.0\cdot10^6$ pm^3, $Z=4$; $R=0.101$ for 3817 independent reflections ($F_0>3.92\sigma(F_0)$).—**2a**: $P\bar{1}$, $a=1058.7(8)$, $b=1342.3(10)$, $c=3733.9(28)$ pm, $\alpha=92.38(6)$, $\beta=97.72(6)$, $\gamma=110.06(6)°$, $V=4917.5\cdot10^6$ pm^3, $Z=2$; $R=0.104$ for 4835 independent reflections ($F_0>3.92\sigma(F_0)$). Both measurements were carried out with a Syntex $P2_1$ diffractometer and $Mo_{K\alpha}$ radiation. Further details of the crystal structure investigations are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD 50869, the names of the authors, and the journal citation.

[9] Characteristic IR, Raman, and UV/VIS bands of **1a** (of **2a** in brackets): IR (CsI): weak bands of the ν(S–S) vibrations at 468, 455 and 437 cm^{-1} (484 and 456 cm^{-1}); *Raman* (solid state, $\lambda_e=647.1$ nm): ν(S–S) = 469, 435, 425 cm^{-1}; further bands at 287, 252, 198, 148 cm^{-1} (ν(S–S) 485, 452, 406 cm^{-1}; further bands at 287, 258, 223, 204 cm^{-1}); ν(S–S) bands, all strong (except that at 485 cm^{-1} (m)), the others with weak to moderate intensity; UV/VIS (reflection; cellulose as standard): $\lambda=325$ nm (340, ca. 470 nm (sh)).

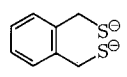
[10] $[Cu_3(S_4)_3]^{3\ominus}$ was detected alongside $[Cu_4(S_4)_3]^{\ominus}$ in a matrix of $[(C_6H_5)_4P]_2[Cu_4(S_4)_3]$: G. Henkel, P. Betz, B. Krebs, Chemiedozententagung, Konstanz 1984; cited in P. Betz, B. Krebs, G. Henkel, *Angew. Chem. 96* (1984) 293; *Angew. Chem. Int. Ed. Engl. 23* (1984) 311.

[11] G. Marbach, J. Strähle, *Angew. Chem. 96* (1984) 229; *Angew. Chem. Int. Ed. Engl. 23* (1984) 246 (see also [2]).

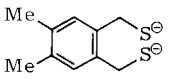
Thiolate Chemistry of the Iron Group Elements: Synthesis and Structure of the Complexes $[Co_2\{o\text{-}(SCH_2)_2C_6H_4\}_3]^{2\ominus}$ and $[Ni_3\{o\text{-}(SCH_2)_2C_6H_4\}_4]^{2\ominus}$**

By *Wolfgang Tremel, Bernt Krebs,* and *Gerald Henkel**

The trinuclear clusters **1**—**4**[1,2] as well as the thiolate ions **5** and **7**[2,3], i.e. both metal thiolate sulfides and pure metal thiolates, could be isolated from the reaction system $MCl_2/X/Y$ [M = Fe, Co, Ni; X = *o*-xylene-α,α′-dithiolate (S_2-*o*-$xyl^{2\ominus}$), durene-α,α′-dithiolate (S_2-$dur^{2\ominus}$); Y = $S^{2\ominus}$, S, $SPh^{\ominus}$, S_2-*o*-$xyl^{2\ominus}$, 1,1-dithiolate]. Complexes containing both thiolate and $S_n^{2\ominus}$-ligands ($n \geq 2$) were hitherto unknown[15].



S_2-*o*-$xyl^{2\ominus}$



S_2-$dur^{2\ominus}$

$[Fe_3S(S_2\text{-}dur)_3]^{2\ominus}$ **1**
$[M_3S(S_2\text{-}o\text{-}xyl)_3]^{2\ominus}$ **2**, M = Fe; **3**, M = Co; **4**, M = Ni
$[M_2(S_2\text{-}o\text{-}xyl)_2(SPh)_2]^{2\ominus}$ **5**, M = Fe; **6**, M = Mn
$[M_2(S_2\text{-}o\text{-}xyl)_3]^{2\ominus}$ **7**, M = Fe; **8**, M = Mn
$[M_2(S_2\text{-}o\text{-}xyl)_2(R_2dtc)_2]^{2\ominus}$ **9**, M = Fe; **10**, M = Mn

The Fe_3S_4 skeleton of **1** and **2** is, together with the analogous fragment of the mixed valent cluster $[Fe_6S_9(SR)_2]^{4\ominus}$[4], of interest as a structural model of the centers in [3 Fe-4S]-proteins[5]. The studies were extended to manganese, the first result being the synthesis of the manganese complexes **6** and **8**, the analogues of **5** and **7**, respectively[6]. The thiophenolate species **5** and **6** can be derivatized to give the anions **9** and **10**, respectively ($R_2dtc^{\ominus}$ = dialkyldithiocarbamate)[7], in which the monodentate $PhS^{\ominus}$ group is replaced by a bidentate $R_2dtc^{\ominus}$ group. We were also able to isolate the novel thiolate ions $[Co_2(S_2\text{-}o\text{-}xyl)_3]^{2\ominus}$ **11** and $[Ni_3(S_2\text{-}o\text{-}xyl)_4]^{2\ominus}$ **13**.

$[Co_2(S_2\text{-}o\text{-}xyl)_3]^{2\ominus}$ **11**
$[Me_4N]_2[Co_2(S_2\text{-}o\text{-}xyl)_3]\cdot 5\,MeOH$ **12**

The binuclear anion **11**, which is isostructural with **7** (Fig. 1), is formed on reaction of $CoCl_2$ with S_2-*o*-$xyl^{2\ominus}$ (in the ratio 2:3) in methanol and precipitates as the crystalline salt **12** on addition of Me_4NCl[8,9]. The Co_2S_6 center of **11**, as a section of the M_3S_7 center of **1**, **2** or **3**, consists of edge-sharing MS_4 tetrahedra, one of the three S_2-*o*-$xyl^{2\ominus}$ groups not functioning as a chelate ligand but spanning the Co_2S_4 fragment in a handle-like fashion. The S atoms of this group thus occupy opposite terminal coordination sites of the Co_2S_6 center. The rigid 1,4-dithiolate ligand cannot bridge a planar $Co_2(\mu\text{-}S)_2$ moiety. The S5...S6 distance within this ligand (4.264(3) Å) leads to a folding of the moiety along the S2...S4 vector and, thus, to a concomitant lengthening of the distance between the corresponding terminal atoms S1 and S3 (6.629(3) Å). The folding of the $M_2(\mu\text{-}S)_2$ moiety in **7** and **11** leads to a significant shortening of the metal-metal distance by ca. 0.1 Å

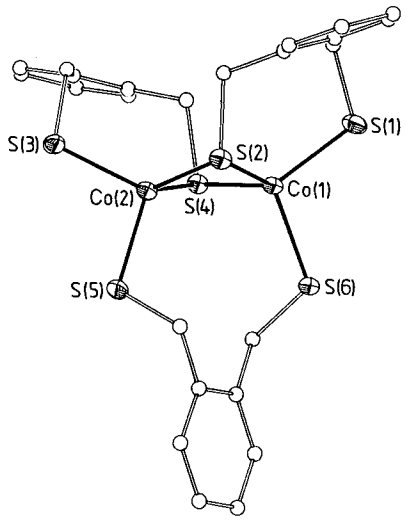


Fig. 1. Structure of the anion **11** in the crystal of **12** with thermal ellipsoids of the Co and S atoms (50% probability, without H atoms, −130°C). Important bond lengths [Å]: Co1...Co2 2.786(1), S1...S3 6.629(3), S5...S6 4.264(3), Co1-S1 2.271(2), Co1-S2 2.294(2), Co1-S4 2.290(2), Co1-S6 2.308(2), Co2-S3 2.261(2), Co2-S2 2.310(2), Co2-S4 2.299(2), Co2-S5 2.306(2); range of angles [°]: S-Co-S 99.77(8) to 122.20(8); Co-S-Co 74.47(7) and 74.74(7).

with respect to comparable complexes with a planar $M_2(\mu\text{-}S)_2$ structure[2,10]. The mean M-S and M-M distances of 2.292 and 2.786 Å in **11** are about 0.04 and 0.09 Å shorter than in the analogous Fe complex **7**, which corresponds to the sums of the ionic radii (Co^{II} 0.72, Fe^{II} 0.77 Å[11]). In principle, three isomers are possible in the case of complexes with non-planar $M(\mu\text{-}SR)_2M$ moieties. Due to the restrictive geometry of the S_2-*o*-$xyl^{2\ominus}$ ligands, **7** and **11** belong to the rare *syn-exo*-type complexes[12].

$[Ni_3(S_2\text{-}o\text{-}xyl)_4]^{2\ominus}$ **13**
$[Et_4N]_2[Ni_3(S_2\text{-}o\text{-}xyl)_4]\cdot 2\,MeOH$ **14**

Reaction of $NiCl_2$ with S_2-*o*-$xyl^{2\ominus}$ in the ratio 1:2 to 1:4 in methanol leads to formation of the trinuclear cluster ion

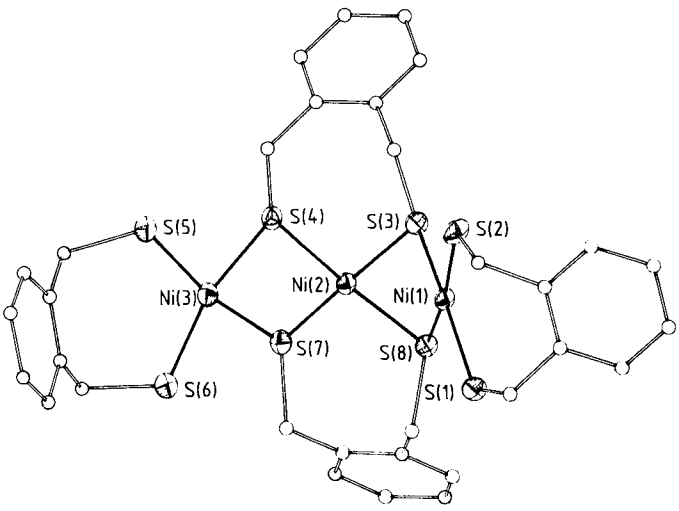


Fig. 2. Structure of the anion **13** in the crystal of **14** with thermal ellipsoids of the Ni and S atoms (50% probability, without H atoms, −130°C: Important bond lengths [Å]: Ni1...Ni2 3.131(1), Ni2...Ni3 3.016(1), S3...S8 2.687(2), S4...S7 2.735(2), Ni1-S1 2.185(2), Ni1-S2 2.177(2), Ni1-S3 2.228(2), Ni1-S8 2.226(2), Ni2-S3 2.206(2), Ni2-S4 2.193(2), Ni2-S7 2.208(2), Ni2-S8 2.192(2), Ni3-S5 2.185(2), Ni3-S6 2.193(2), Ni3-S4 2.219(2), Ni3-S7 2.229(2); range of angles [°]: Ni1...Ni2...Ni3 131.34(4), S-Ni-S(*cis*) 74.22(7) to 105.19(8), S-Ni-S(*trans*) 164.01(8) to 173.34(8), Ni-S-Ni 85.66(7) to 90.26(7).

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13 (Fig. 2), which crystallizes as the salt **14**[8,9]. The metal-sulfur skeleton of **14** resembles the corresponding moiety of the cyclic complex $[Ni(SEt)_2]_6$[13]. The three Ni atoms in **13** are arranged at an angle of 131.34(4)°, with four of the eight S atoms lying above and the other four lying below the plane of the metal atoms. The coordination of each Ni atom is approximately square-planar. In the center of the cluster, Ni2 is surrounded by the S atoms of two chelate ligands at a distance of 2.200 Å (mean value), which, as μ_2-substituents, form bridges (mean Ni-S 2.226 Å) to the terminal Ni atoms. The coordination of these metal centers is completed by the S atoms of terminally bonded chelate ligands (mean Ni-S 2.185 Å). Like **11**, **13** is also folded along the S...S vectors of the $M_2(\mu\text{-}S)_2$ moieties, whereby the distances S4...S7 (2.735(2) Å) and S3...S8 (2.687(2) Å) are strikingly short. Interactions due to oxidative S...S coupling and involving partial metal reduction could be in effect here[12]. The Ni-Ni distances lie outside of the range for direct metal-metal interactions. The Ni-S-Ni valence angles are about as large as in the cyclic compound $[Ni(SEt)_2]_6$[13].

Thus, it emerges that there are pronounced structural analogies in polynuclear thiolate- and thiolate-sulfide complexes of the electron-rich bivalent transition metals.

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[1] G. Henkel, W. Tremel, B. Krebs, *Angew. Chem. 93* (1981) 1072; *Angew. Chem. Int. Ed. Engl. 20* (1981) 1033; K. S. Hagen, G. Christou, R. H. Holm, *Inorg. Chem. 22* (1983) 309; G. Henkel, W. Tremel, B. Krebs, *Angew. Chem. 95* (1983) 314; *Angew. Chem. Int. Ed. Engl. 22* (1983) 318; *Angew. Chem. Suppl. 1983,* 307; W. Tremel, B. Krebs, G. Henkel, *Inorg. Chim. Acta Lett. 80* (1983) 31.

[2] G. Henkel, W. Tremel, B. Krebs, *Angew. Chem. 95* (1983) 317; *Angew. Chem. Int. Ed. Engl. 22* (1983) 319; *Angew. Chem. Suppl. 1983,* 323.

[3] R. W. Lane, J. A. Ibers, R. B. Frankel, G. C. Papaefthymiou, R. H. Holm, *J. Am. Chem. Soc. 99* (1977) 84; it follows from a footnote in [10] that the compound of composition $[Fe_2(S_2\text{-}o\text{-}xyl)_3]^{2\ominus}$ described by *Lane* et al. is an isomer of **7**.

[4] G. Henkel, H. Strasdeit, B. Krebs, *Angew. Chem. 94* (1982) 204; *Angew. Chem. Int. Ed. Engl. 21* (1982) 201; *Angew. Chem. Suppl. 1982,* 489; H. Strasdeit, B. Krebs, G. Henkel, *Inorg. Chem. 23* (1984) 1816; G. Christou, M. Sabat, J. A. Ibers, R. H. Holm, *ibid. 21* (1982) 3518; K. S. Hagen, A. D. Watson, R. H. Holm, *J. Am. Chem. Soc. 105* (1983) 3905.

[5] M. K. Johnson, R. S. Czernuszewicz, T. G. Spiro, J. A. Fee, W. V. Sweeney, *J. Am. Chem. Soc. 105* (1983) 6671.

[6] K. Greiwe, B. Krebs, G. Henkel, unpublished.

[7] W. Tremel, K. Greiwe, B. Krebs, G. Henkel, unpublished; G. Henkel, W. Tremel, U. Kuhlmann, B. Krebs, *Int. Conf. Coord. Chem. 21st, 1980,* Abstr. 351.

[8] Experimental (all operations carried out under N_2 in degassed solvents): **12**: A solution of $CoCl_2 \cdot 6H_2O$ (4.76 g, 20 mmol) in methanol (50 mL) was treated dropwise with a solution of sodium (1.38 g, 60 mmol) and *o*-xylenedithiol (5.10 g, 30 mmol) in methanol (60 mL). The mixture was stirred overnight, evaporated at room temperature in vacuo to ca. 70% of its original volume, treated with 2.20 g (20 mmol) solid Me_4NCl, and cooled to −30°C. After a few days, greenish-brown crystals of **12** precipitated (yield 4.6 g, 55%).—**14**: A suspension of $NiCl_2$ (3.91 g, 30 mmol) in methanol (50 mL) was treated with a solution of sodium (1.38 g, 60 mmol) and *o*-xylenedithiol (5.1 g, 30 mmol) in methanol (60 mL). When the initial precipitate was treated with a solution of sodium (0.69 g, 30 mmol) and thiophenol (3.1 mL, 30 mmol) in methanol a blackish-brown solution was obtained, from which, on addition of 4.97 g (30 mmol) Et_4NCl, black crystals of **14** separated in the course of a few days. **14** was recrystallized from dimethylformamide/MeOH, yield: 2.7 g (37%); $\lambda(\varepsilon)$ [nm]: 356 (14900), 423 (8000).

[9] Crystal structure analysis: **12**: $P2_1/n$, $a = 13.651(3)$, $b = 15.629(3)$, $c = 22.552(5)$ Å, $\beta = 105.18(2)°$, $Z = 4$, $\rho_{calc} = 1.332$ g cm^{-3}, $\mu(Mo_{K\alpha}) = 10.4$ cm^{-1}, 7322 reflections, 4921 observed ($F_o > 3.92\sigma(F_o)$; isotypic with $[Me_4N]_2[Fe_2(S_2\text{-}o\text{-}xyl)_3] \cdot 5\,MeOH$ [2]; 453 variables; $R(R_w) = 0.066$ (0.064).—**14**: $P\bar{1}$, $a = 13.131(3)$, $b = 15.148(4)$, $c = 16.694(4)$ Å, $\alpha = 110.26(3)$, $\beta = 99.41(3)$, $\gamma = 110.25(3)°$. $Z = 2$, $\rho_{calc} = 1.409$ g cm^{-3}, $\mu(Mo_{K\alpha}) = 13.4$ cm^{-1}, 8497 reflections, 6777 observed (vide supra), 586 variables, $R(R_w) = 0.058$ (0.059). Syntex $P2_1$ four-circle diffractometer; graphite monochromator, scintillation counter, 2θ-scan, $2\theta_{max} = 48°$; −130°C; empirical absorption corrections, refinement of the non-H atoms (with exception of disordered solvent molecules) with anisotropic temperature factors (block diagonal matrix least squares); H atoms calculated or from difference Fourier syntheses, all H atom coordinates fixed ($B = 5.0$ Å^2); further details of the crystal structure investigations are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD 50963, the names of the authors, and the journal citation.

[10] K. S. Hagen, R. H. Holm, *J. Am. Chem. Soc. 104* (1982) 5496.

[11] R. D. Shannon, *Acta Crystallogr. A 32* (1976) 751.

[12] J. P. Fackler, Jr., *Prog. Inorg. Chem. 21* (1976) 55.

[13] P. Woodward, L. F. Dahl, E. W. Abel, B. C. Crosse, *J. Am. Chem. Soc. 87* (1965) 5251; E. W. Abel, B. C. Crosse, *J. Chem. Soc. A 1966,* 1377.

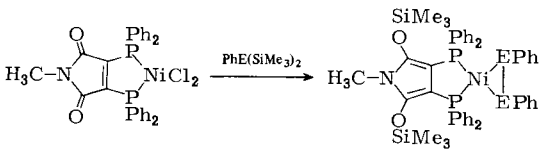
[14] Lane et al. describe a complex $[Et_4N]_2[Ni_2(S_2\text{-}o\text{-}xyl)_3]$ [3] which was obtained in a similar way.—However, it differs from **13** in its spectroscopic properties.

[15] *Note added in proof (July 13, 1984):* Following the synthesis of the X-ray crystallographically characterized complex salt $(PPh_4)_2[Ni_4(S)_2(SCH_2CH_2S)_4] \cdot MeOH$, we have in the meantime succeeded in gaining access to the first mixed thiolate-disulfide complex anion.

The Reaction of [2,3-bis(diphenylphosphino)-*N*-methylmaleimide]nickel(II) Chloride with $PhE(SiMe_3)_2$ (E = P, As)**

By *Dieter Fenske** and *Kurt Merzweiler*

Phosphane complexes of $NiCl_2$ react with silylated phosphanes in various ways. For example, diphosphene complexes are obtained in the reaction of $(R_3P)_2NiCl_2$ ($R = C_2H_5$) and $LiP(SiMe_3)_2$[1]. In contrast, the reaction of $NiCl_2$ and PPh_3 with $PhP(SiMe_3)_2$ leads to $Ni_8X_4(PPh_3)_4(\mu_4\text{-}PPh)_6$ ($X = Cl^{\ominus}$, CO)[2]. To prepare clusters of this type with bidentate phosphane ligands, we allowed the $NiCl_2$ complex **1**[3] of 2,3-bis(diphenylphosphino)-*N*-methylmaleimide to react with $PhP(SiMe_3)_2$. In this way, the yellow diphosphene complex **2** is formed in 60% yield[4]. Under analogous conditions, reaction of **1** and $PhAs(SiMe_3)_2$ affords a compound isostructural to **2** with a PhAs=AsPh ligand[4].



1 **2**, E = P; **3**, E = As

According to ^{31}P-NMR spectroscopic studies, the silylphosphane reacts initially with the maleimide ligand. The diphosphene moiety at the nickel is presumably formed subsequently via a complex with two terminal $PhP(SiMe_3)$ groups, by analogy to reactions of $(R_2PCH_2CH_2PR_2)NiCl_2$ with $LiP(SiMe_3)_2$ and $R'P(SiMe_3)_2$[5] (R = Et, *cyclo*-C_6H_{11}; R' = Me, Ph, *t*Bu).

In the IR spectra of **2** and **3**, ν(C=C) bands are observed at 1542 and 1522, and 1534, 1555, and 1572 cm^{-1}, respectively. In the ^{31}P-NMR spectrum of **2**, the P atoms of the PPh_2 and PPh ligands exhibit a triplet ($J_{PP} = 30$ Hz) at $\delta = +36.5$ and -4.9, respectively[6].

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[**] This work was supported by the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie, and the Institut für Kristallographie (crystallographic data). We thank Prof. Dr. *H. Schäfer* (Karlsruhe) for assistance in the discussion of the ^{31}P-NMR spectra.

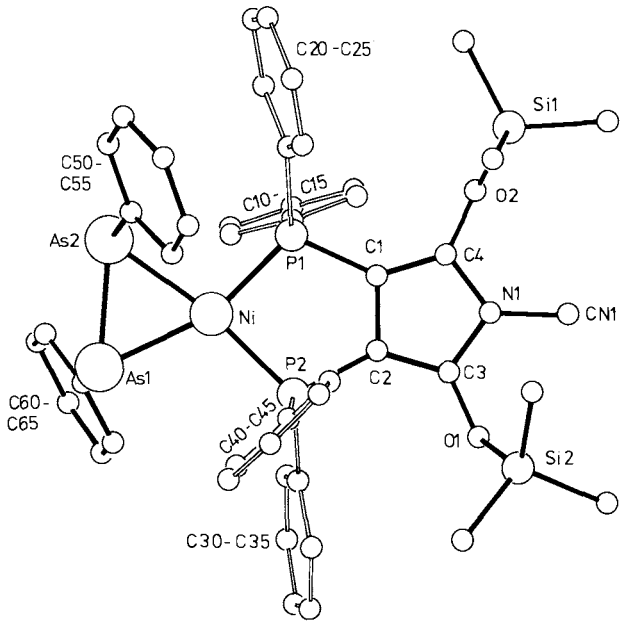
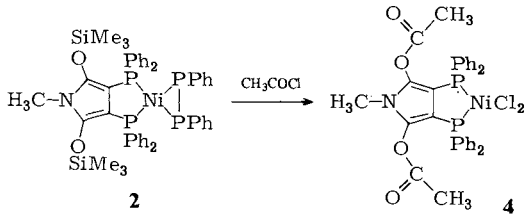


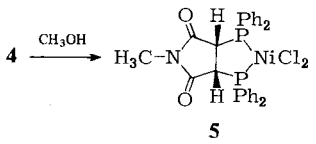
Fig. 1. Molecular structure of **3** [8] in the crystal [13]. Important bond lengths [pm]: Ni-P 214–215.0(2), Ni-As1 236.0(1), Ni-As2 236.4(1), As1-As2 237.2(1), C1-C2 145.9(9), C2-C3 137.1(9), C-O 134.5(8), C-N 139.6(8), C1-C4 135.5(8), Si-O 169.0(2), Si-C 185.0(1), As1-C60 199.0(8), As2-C50 197.0(7); important bond angles [°]: P1-Ni-P2 92.9(1), As2-Ni-P1 100.5(1), As1-Ni-P2: 106.7(1), As1-Ni-P1 160.4(1), As2-Ni-P2 160.0(1), As2-Ni-As1 59.9(1), Ni-As1-As2 59.9(1), As2-As1-Ni 59.8(1), C60-As1-Ni 90.9(2), C50-As2-Ni 95.0(1), As2-As1-C60 93.4(2), As1-As2-C50 101.0(2). Important bond lengths [pm] and bond angles [°] for the analogous structure of **2** [7]: Ni-P1 215.4(1), Ni-P2 215.7(1), Ni-P3 225.7(1), Ni-P4 225.3(1), P3-P4 214.0(1), the remaining bond lengths correspond to those of **3**, within the standard deviation. P1-Ni-P2 92.9(1), P4-Ni-P1 159.0(1), P2-Ni-P4 106.8(1), P1-Ni-P3 105.0(1), P2-Ni-P3: 160.9(1), P3-Ni-P4 56.7(1), Ni-P3-P4 61.6(1), Ni-P4-P3 61.8(1), Ni-P3-C50 94.6(1), Ni-P4-C60 99.5(1), P4-P3-C50 100.7(1), P3-P4-C60 101.3(1) (P3 ≙ As2; P4 ≙ As1).

The crystal structure analysis indicated that **2**[7] and **3** (Fig. 1)[8] have practically the same molecular structure. In the diarsene complex **3**, the Ni is approximately planar-coordinated by the As atoms of the PhAs=AsPh ligand and by the P atoms of the PPh_2 groups. With 214.0(1) and 237.2(3) pm, respectively, the P–P and As–As distances in the PhE=EPh ligands of **2** and **3** are markedly shorter than an E–E single bond and correspond to the values found in other complexes with side-on coordinated PhE=EPh[9].

The PhE=EPh ligand in **2** and **3** has a *trans*-configuration, and the atoms C50-P3-P4-C60 and C50-As2-As1-C60 are almost coplanar. The dihedral angles C50-P3-P4-C60 and C50-As2-As1-C60 are 175.7° and 178.3°, respectively. If it is assumed that Ni^0 is involved, together with the two PPh_2 and the PhE=EPh ligands Ni has a total of 16 valence electrons. As a consequence of the $SiMe_3$-transfer to the CO group of the *N*-methylmaleimide, a PPh_2-substituted derivative of 2,5-bis(trimethylsiloxy)-*N*-methylpyrrole is formed. This can be seen clearly from the bond lengths in the planar five-membered ring. Reaction of **2** and CH_3COCl leads to formation of the red acyl derivative **4**; simultaneously, the diphosphane ligand is displaced and the Ni^0 oxidized to $Ni^{2\oplus}$.

The IR spectrum of **4** exhibits a ν(CO) band at 1782 cm^{-1} and a band for ν(C=C) at 1542 cm^{-1}. On the basis of the crystal structure analysis, Ni is coordinated in a distorted square-planar manner by two P atoms and two $Cl^{\ominus}$[10]. The Cl ligands lie respectively 48 pm above and below the plane formed by the Ni and P atoms. As in **2** and **3**, the pyrrole ring is planar.





With CH_3OH, **4** undergoes hydrolysis and rearrangement to yield **5**. Presumably **5** is formed via an unstable derivative of 2,5-dihydroxypyrrole which isomerizes via keto-enol tautomerism. This observation corresponds to the fact that hydroxypyrrole can also readily rearrange to the keto form[11]. As shown by the crystal structure analysis, the H-shift gives rise to the *cis*-isomer **5**[12]. Ni is planar coordinated by the two P atoms and two $Cl^{\ominus}$ ligands; one P atom lies 88 and the other 188 pm above the mean plane of the succinimide ring. **5** can also be formed from **2** by recrystallization from a mixture of $1,2\text{-}C_2H_4Cl_2$ and CH_3OH.

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[1] H. Schäfer, *Z. Naturforsch. B 34* (1979) 1358.
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[3] H. J. Becher, W. Bensmann, D. Fenske, *Chem. Ber. 110* (1977) 315.
[4] Procedure: **1** (11.4 g, 0.0187 mol) is dissolved in 100 mL tetrahydrofuran (THF) under N_2 and treated with $PhP(SiMe_3)_2$ (9.7 g, 0.038 mol). Within a few minutes, a dark brown solution is formed. After 12 h the solvent is removed and the residue dissolved in 100 mL toluene. **2** precipitates out as fine crystals (yield ≈60%); crystallization from toluene affords yellow crystals.—**3**: By analogy to **2** from **1** (11.1 g, 0.0182 mol) and $PhAs(SiMe_3)_2$ (11 g, 0.037 mol). **3** precipitates out from toluene as red crystals (yield 50%).—**4**: By analogy to **2**; after the residue has been taken up in toluene, CH_3COCl (10 mL) is added. **4** then precipitates in 70% yield. Crystallization from $1,2\text{-}C_2H_4Cl_2$/acetone affords deep-red crystals.—**5**: **4** (3.48 g, 0.005 mol) is dissolved in 100 mL $1,2\text{-}C_2H_4Cl_2$ and 10 mL CH_3OH added. **5** precipitates out as fine crystals (yield 80%).
[5] H. Schäfer, D. Binder, unpublished.
[6] It cannot be distinguished whether the two multiplets involve a genuine triplet of an A_2X_2 system with $cis\text{-}^2J_{PP} = trans\text{-}^2J_{PP}$ or two pseudo-triplets of an AA'XX' spin system with $|cis\text{-}^2J_{PP} + trans\text{-}^2J_{PP}| = 60$ Hz and $^1J_{PP} > 300$ Hz.
[7] **2** (180 K): $a = 1227.3(4)$, $b = 1463.5(6)$, $c = 1521.6(7)$ pm, $\alpha = 108.11(3)$, $\beta = 96.46(3)$, $\gamma = 113.38(3)°$, space group $P\bar{1}$, $Z = 2$, $\mu(Mo_{K\alpha}) = 6.98$ cm^{-1}; Syntex R3, $Mo_{K\alpha}$, up to $2\theta = 56°$, 11562 reflections, 10497 of which with $I > 2\sigma(I)$; structure solved using Patterson methods, all atoms (except Ph–H) refined anisotropically, leading to $R_1 = 0.041$, $R_2 = 0.045$.
[8] **3** (180 K): $a = 1187.4(4)$, $b = 1846.4(7)$, $c = 2176.4(9)$ pm, $\beta = 105.16(3)°$; space group $P2_1/n$, $Z = 4$, $\mu(Mo_{K\alpha}) = 20.0$ cm^{-1}; Syntex R3, $Mo_{K\alpha}$, up to $2\theta = 55°$, 11233 reflections, 8648 of which with $I > 2\sigma(I)$, empirical absorption correction; structure solved using Patterson methods, all atoms refined anisotropically (H isotropically), leading to $R_1 = 0.068$, $R_2 = 0.066$.
[9] I. Borm, L. Zsolnai, G. Huttner, *Angew. Chem. 95* (1983) 1018; *Angew. Chem. Int. Ed. Engl. 22* (1983) 977; *Angew. Chem. Suppl. 1983*, 1477; and literature cited therein; B. Deppisch, H. Schäfer, *Acta Crystallogr. Sect. B 38* (1982) 748; H. Vahrenkamp, D. Wolters, *Angew. Chem. 95* (1983) 152; *Angew. Chem. Int. Ed. Eng. 22* (1983) 154; H. Chatt, P. Hitchcock, A. Pidcock, C. P. Warrens, K. R. Dixon, *J. Chem. Soc. Chem. Commun. 1982*, 932.

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[10] **4** (180 K): $a=2207.0(10)$, $b=9503.0(5)$, $c=1540.0(9)$ pm; space group $Pna2_1$, $Z=4$, $\mu(Mo_{K\alpha})=9.2$ cm^{-1}; Syntex R3, $Mo_{K\alpha}$, up to $2\theta=55°$, 5104 reflections, 3902 of which with $I>2\sigma(I)$, empirical absorption correction; structure solved using Patterson methods, all atoms refined anisotropically (H isotropically), leading to $R_1=0.043$, $R_2=0.042$.—Important bond lengths [pm] (numbering of the atoms ≙ **3** in Fig. 1): Ni-P1 217.7(1), Ni-P2 213.0(1), Ni-Cl1 220.3(1), Ni-Cl2 220.9(1), C1-C2 142.5(7), C2-C3 135.1(7), C3-N1 138.3(6), N1-C4 138.7(7), C4-C1 136.5(6), C3-O1 137.8(6), C2-O2 136.3(6); important bond angles [°]: P1-Ni-P2 90.5(1), P1-Ni-Cl1 167.1(1), P2-Ni-Cl1 88.7(1), P1-Ni-Cl2 89.2(1), P2-Ni-Cl2 167.7(1), Cl1-Ni-Cl2 94.3(1).

[11] A. R. Katritzky, *Chimia 24* (1970) 134; H. Plieninger, M. Decker, *Justus Liebigs Ann. Chem. 598* (1956) 198.

[12] **5** (180 K): $a=1465.3(6)$, $b=1863.4(7)$, $c=2308.6(9)$ pm; space group Pbca, $Z=8$, $\mu(Mo_{K\alpha})=7.6$ cm^{-1}; Syntex R3, $Mo_{K\alpha}$, up to $2\theta=50°$, 5805 reflections, 4116 of which with $I>2\sigma(I)$, empirical absorption correction; structure solved using Patterson methods, all atoms refined anisotropically (H isotropically), leading to $R_1=0.058$, $R_2=0.054$.—Important bond lengths [pm]: (numbering of atoms ≙ **3** in Fig. 1): Ni-P 214.0(2), Ni-Cl 219.6—220.8(2), C1-C2 153.7(9), C2-C3 151.8(9), C3-N1 138.0(9), N1-C4 138.1(8), C4-C1 153.0(9), C3-O1 121.1(8), C4-O2 120.5(8), C1-HC1 96.0(30), C2-HC2 99.0(35); important bond angles [°]: P1-Ni-P2 89.6(1), P1-Ni-Cl1 89.0(1), P2-Ni-Cl1 169.0(1), P1-Ni-Cl2 169.9(1), P2-Ni-Cl2 88.4(1), Cl1-Ni-Cl2 94.9(1).

[13] Further details on the crystal structure investigation can be obtained from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, by quoting the depository number CSD 50908, the names of the authors, and the journal citation.

Transallenation of 1,3-Bis(dialkylamino)-1,3-diethoxyallenes with Disubstituted Malonyl Chlorides**

By *Rolf W. Saalfrank**, *Walter Rost*, *Franz Schütz*, and *Ulrike Röss*

Tetraethoxyallene **1a**—synthetic equivalent of the dianion of diethyl malonate—reacts with phosgene to afford bis(ethoxycarbonyl)ketene and with succinyl chloride and its higher homologues to give lactones[1]. However, an attempt to convert malonyl chloride into diethyl (4-oxo-2-oxetanylidene)malonate was unsuccessful due to the acidity of the methylene protons of malonyl chloride.

We have now allowed **1a**[2] to react with oxalyl chloride **2** and with the dialkylmalonyl chlorides **6a—c**, thereby obtaining 3-chloro-4-(ethoxycarbonyl)maleic anhydride **3** (yield 60%; m.p. = 76 °C) and the diethyl (3,3-dialkyl-4-oxo-2-oxetanylidene)malonates **8a—c** (yields 88, 68, 73%; m.p. = 43 °C, b.p. = 88 °C/0.05 torr, m.p. = 43 °C).

The constitution of the novel anhydride **3** is based on its spectroscopic data and on its Diels-Alder reaction with 2,3-dimethyl-1,3-butadiene **4** to afford 1-chloro-2-(ethoxycarbonyl)-4,5-dimethyl-4-cyclohexene-1,2-dicarboxylic acid anhydride **5** (yield 86%, m.p. = 54 °C).

The oxetanones **8** are "mixed ketene dimers", only a few examples of which are known[5].

The spectra of **8a—c** are as expected. In contrast, the ^{1}H- and ^{13}C-NMR spectra of the oxetanones **8d—g** (yields 61, 51, 52, 64%; m.p. = 83, 92, 80, 89 °C), obtained from 1,3-bis(dialkylamino)-1,3-diethoxyallenes **1b**, **c**[6], and dialkylmalonyl chlorides **6a**, **c** are temperature dependent. Apparently, the C_s symmetry in **8d—g** is perturbed by the steric interactions between the substituents R^2/R^3 and the neighboring dialkylcarbamoyl group.

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[**] 1,3-Donor/Donor-Substituted Allenes in Synthesis, Part 2. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.—Part 1: [1].

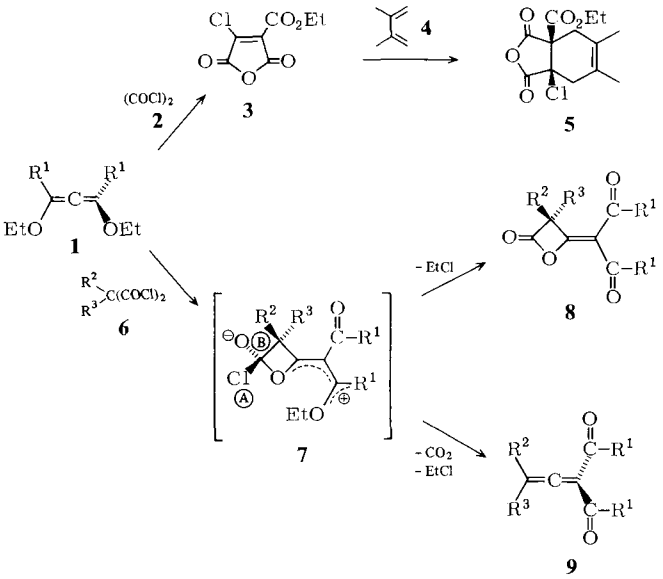
Allene **1b** does not form oxetanones with the malonyl chlorides **6b**, **d**; rather, allenes **9a**, **b** result (yields 52, 61%; m.p. = 75 °C/0.05 torr, m.p. = 177 °C) (Table 1).

Table 1. Spectroscopic data for the allenes **9**.

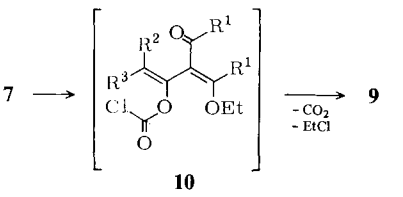
9a, IR (film): 1950 (=C=), 1635 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$): $\delta=1.13$ (t, 6H, CH_3), 2.17 (q, 4H, CH_2), 3.17 (s, 12H, NCH_3); ^{13}C-NMR ($CDCl_3$): $\delta=12.38$ (CH_3), 25.30 (CH_2), 35.37 and 38.86 (NCH_3), 100.47 and 113.42 (=C), 165.36 (C=O), 198.90 (=C=)

9b, IR (KBr): 1950 (=C=), 1635 cm^{-1} (C=O); ^{1}H-NMR (C_6D_6): $\delta=2.63$ (s, 6H, CH_3), 2.73 (s, 6H, CH_3), 7.13 (mc, 6 arom. H); 7.50 (mc, 4 arom. H); ^{13}C-NMR ($CDCl_3$): $\delta=35.43$ and 38.95 (CH_3), 100.35 and 114.79 (=C), 128.38, 128.74 and 133.84 (arom. C), 164.30 (C=O), 202.21 (=C=)

9c, IR (KBr): 1970 (=C=), 1630 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$): $\delta=1.12$ (t, 12H, CH_3), 1.75 (s, 6H, CH_3), 3.36 (q, 8H, CH_2); ^{13}C-NMR ($CDCl_3$): $\delta=12.68$, 14.01 and 17.78 (CH_3), 39.74 and 43.26 (CH_2), 96.65 and 100.04 (=C), 164.90 (C=O), 196.82 (=C=)

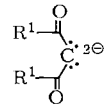
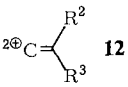


In the reaction of allene **1c** with dimethylmalonyl chloride **6a**, allene **9c** is obtained (yield 21%; m.p. = 68 °C) (Table 1), in addition to **8f**. Since **8f** does not decarboxylate to **9c** under the reaction conditions[9], the betaines **7**[10] can be considered to be the common precursors of **8** and **9**.



Reaction	R^1 (from **1**)	R^2	R^3 (from **6**)
1a + **6a** → **8a**	OEt	Me	Me
1a + **6b** → **8b**	OEt	Et	Et
1a + **6c** → **8c**	OEt	$-(CH_2)_3-$	
1b + **6a** → **8d**	NMe_2	Me	Me
1b + **6c** → **8e**	NMe_2	$-(CH_2)_3-$	
1c + **6a** → **8f** + **9c**	NEt_2	Me	Me
1c + **6c** → **8g**	NEt_2	$-(CH_2)_3-$	
1b + **6b** → **9a**	NMe_2	Et	Et
1b + **6d** → **9b**	NMe_2	Ph	Ph

Depending on the steric interaction between R^1 and R^2/R^3, **7** decomposes to afford **8** (route Ⓐ: cleavage of a C–Cl bond) or the butadienes **10** (route Ⓑ: cleavage of a C–C bond). Spontaneous elimination of CO_2 and ethyl chloride from **10** lead exclusively to the allenes **9**.

11   **12**

Transallenations have previously hardly played a role in the chemistry of allenes. The novel transallenation method leading to the allene-1,1-dicarboxamides **9**[11] is widely applicable given the choice of suitable combinations of substituents. The readily accessible allenes **1b, c** function as synthetic equivalents for the dianions **11** of malonamide, and the disubstituted malonyl chlorides **6a, b, d** as equivalents of 1,1-vinylidene dications **12**.

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CP/MAS-^{13}C-NMR Spectra of Sclerotized Insect Cuticle and of Chitin**

By *Martin G. Peter*, Lothar Grün,* and *Hans Förster*

During the sclerotization of the exoskeleton, which is a vital process for insects, the *N*-acylated catecholamines ("diphenols") *N*-(3,4-dihydroxyphenethyl)acetamide (*N*-acetyldopamine)[1] and 3-amino-*N*-(3,4-dihydroxyphenethyl)propionamide (*N*-β-alanyldopamine)[2] are oxidized in the cuticle to give reactive intermediates. It is thought that such intermediates involve *o*-quinones and/or *p*-quinonemethides, which can lead, in an addition-oxidation-condensation sequence[3], to the covalent cross-linking of proteins and/or chitin[4]. Sclerotized cuticle is almost completely insoluble under nondestructive conditions, and consequently there is no convincing proof for the postulated structures of the cross-linkages[5]. Solid state ^{13}C-NMR spectroscopy has proven most useful for the non-destructive analysis of complex insoluble biopolymers. Using this technique we have now succeeded in obtaining struc-

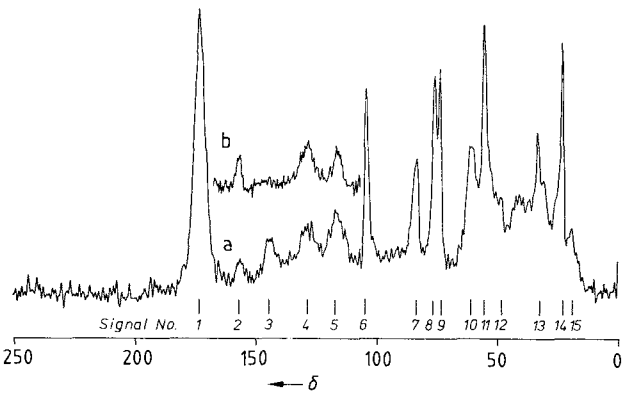

Fig. 1. a) CP/MAS-^{13}C-NMR spectrum of the pupal cases (exuviae) of *Manduca sexta*; b) aromatic region of the CP/MAS-^{13}C-NMR spectrum of *Blaberus giganteus* (exuviae). Spinning side-bands have been suppressed. Conditions of measurement: Bruker CXP 300, at 75.46 MHz, ^{1}H-^{13}C-cross polarization with sample rotation about the magic angle, 15—20 G decoupling field strength, 4.9—5.1 KHz rotation frequency, 1 ms contact time. The sclerotized cuticle was broken down in ice-cold, 0.1 M phosphate buffer (pH 6.8) using an Ultra-Turrax at maximum revolution. After filtration, the sample of cuticle was washed with water, ethanol, and ether, and dried over P_4O_{10}.

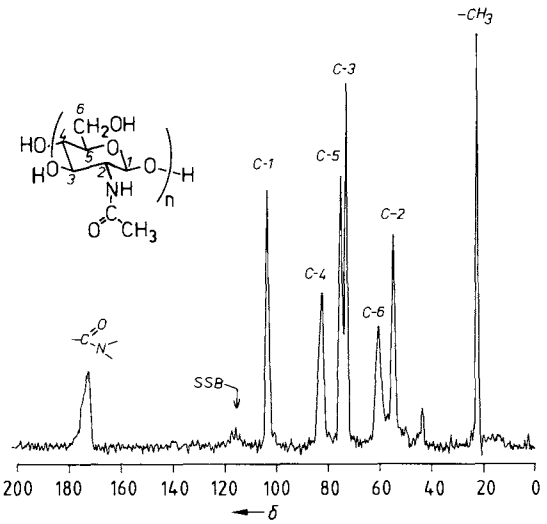

Fig. 2. CP/MAS-^{13}C-NMR spectrum of chitin. Spinning side-bands have not been suppressed. The cuticle of *Manduca sextra* larvae was treated twice in the following way: immersed for 1 h in 10% NaOH at 80°C, washed with water, immersed for 1 h in 98% HCOOH at 22°C, washed with water, dried over P_4O_{10}, remaining chitin cut into smaller pieces with scissors.

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tural information about the completely sclerotized, native cuticle of insects.

Figure 1a shows a CP/MAS-^{13}C-NMR spectrum of solid, deep-brown colored pupal cases (exuviae) of the tobacco hornworm *Manduca sexta*. A comparison of this spectrum and that of chitin (Fig. 2) immediately allows assignment of the signal groups 1, 6 up to 11, and 14 (see Table 1 and [6]), which can be seen to arise from 2-deoxy-2-acetylaminoglucopyranosyl moieties.

Comparison with the spectrum of bovine serum albumin (Fig. 3) reveals a contribution by proteins in the signal groups 1, 2, 4, 5 and 10 to 15 (see Table 1 and [7]). What can now be deduced about the fate of the *N*-acylated catecholamines which are incorporated into the cuticle during sclerotization? In the signal groups 1 and 14 the resonances of the *N*-acetyl groups superimpose those of chitin. The signals of the aliphatic C-atoms of the side-chain, which coincide with those of amino acid residues, are likewise not observable separately. In contrast, the region of aromatic C-atoms has great diagnostic value. Comparison with a solid-state ^{13}C-NMR spectrum of *N*-acetyldopamine[8] reveals that the signal groups 3 and 5 observed in the spectrum of the sclereotized cuticle are mainly derived from diphenolic partial structures. Most likely these are polyphenols formed by oxidative coupling. The absorption regions of the groups 3 and 5 are very much broader than the chitin resonances, thus indicating the presence of a large number of aromatic C-atoms with different chemical environments. The assignment of the signal groups 1 to 4 to quaternary C-atoms also follows from a spectrum that was recorded with a NQS pulse sequence, by which the remaining resonances are suppressed.

The observation that the transformation products of the sclerotizing agents in the cuticle are present in the *reduced* state is at first sight surprising, since it contradicts the hypothesis of a covalent cross-linking of proteins via aminoquinone imines. The absorptions of imino C-atoms are to be expected in the region of $\delta \approx 150-160$. The phenoxy C-atoms of tyrosine and guanidino C-atoms of arginine also appear in this region[7]. A comparison of the intensities of the signal groups 2 in the cuticle spectrum (Fig. 1a) and in the protein spectrum (Fig. 3) with those of the groups 4 gives no indication of larger amounts of aminoquinone imine partial structures. Exuviae of the migratory locust *Locusta migratoria* have an analogous solid state ^{13}C-NMR spectrum. In contrast, in the exuviae of the cockroach *Blaberus giganteus* one finds substantially smaller amounts of diphenols (Fig. 1b). Apparently, the molecular principles of the sclerotization of the cuticle are different in at least this insect species.

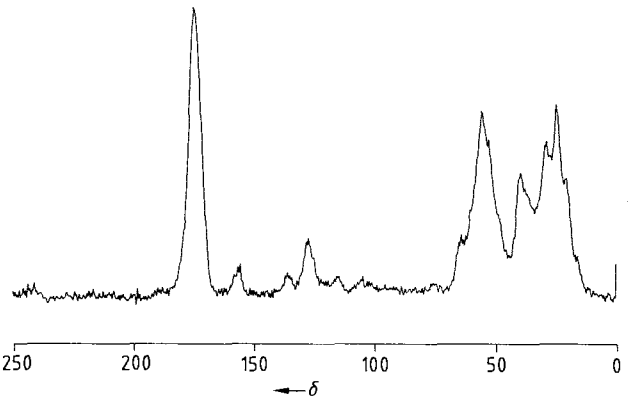

Fig. 3. CP/MAS-^{13}C-NMR spectrum bovine serum albumin (Sigma). Spinning side-bands were suppressed. Conditions of measurement as in Fig. 1.

Table 1. Assignment of the signal groups in the CP/MAS-^{13}C-NMR spectra of sclerotized cuticle (Fig. 1), of chitin (Fig. 2) and of bovine serum albumin (Fig. 3).

Signal group	δ-Values (rel. Int.) of the signal centers			Assignment
	Cuticle	Chitin	Protein	
1	171.6 (vs)	172 (m)	176.3 (vs)	Acylamine in chitin and protein
2	154.8 (vw)	—	158.8 (vw)	Phenoxy-C in tyrosin, guanidino-C in arginine
3	143.6 (w)	—	—	Phenoxy-C in diphenols
4	128.9 (m)	—	129 (m)	aromat. C
5	115.6 (s)	115 [a] (vw)	115.5 (vw)	C-3/5 in tyrosin, C-4 in imidazole, C-2/5 in diphenols
6	103.5 (vs)	102.3 (s)	—	C-1 in β-GlcNAc moieties
7	82.3 (s)	82.3 (s)	—	C-4 in β-GlcNAc moieties
8	75.3 (vs)	73.9 (vs)	—	C-5 in β-GlcNAc moieties
9	73.6 (vs)	71.6 (vs)	—	C-3 in β-GlcNAc moieties
10	60.0 (s)	60.0 (s)	65 (m)	C-6 in β-GlcNAc moieties, α-C in amino acid residues
11	54.8 (vs)	53.6 (s)	57 (s)	C-2 in β-GlcNAc moieties, α-C in amino acid residues
12	44.2 (s)	44.1 [b] (vw)	41 (s)	aliph. C in amino acid residues
13	32.8 (s)	—	30 (s)	aliph. C in amino acid residues
14	23.4 (vs)	22.1 (vw)	25/21 (vs)	CH_3 in acetyl, CH in leucine and isoleucine
15	19.3 (s)	—	18 (m)	CH_3 in alanin and leucine

[a] Spinning side-band of group 1. [b] Chitin cannot be obtained completely free of protein.

The question whether covalent protein-diphenol linkages are formed by addition of nucleophiles to *p*-quinomethides cannot be answered without the use of isotopically labeled compounds.—The above results are consistent with the hypothesis that the sclerotization of the cuticle occurs by a denaturation of structure proteins by polyarenes. This would suggest analogies to the tanning of proteins by catechin-type polymers or to the stabilization of plant structures by lignin[9].

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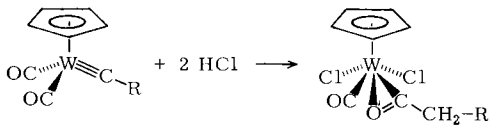
Acid-Induced Carbyne-Acyl Rearrangement—an Unexpected CC Coupling Reaction**

By *Fritz R. Kreissl**, *Werner J. Sieber*, *Mathias Wolfgruber*, and *Jürgen Riede*

In the homogeneous- or heterogeneous-catalyzed reduction of carbon monoxide, carbene, carbyne, or carbide ligands are thought to be linked intramolecularly to coordinated CO[1,2]. Examples are 1) the thermal decomposition of diphenylcarbene complexes of chromium and tungsten[3], 2) the base-induced, intramolecular carbonylation of dicarbonyl(η^5-cyclopentadienyl)carbene complexes of molybdenum and tungsten[4], as well as 3) the carbonylation of carbide clusters[5].

We have now obtained the η^2-acyl complexes **2a**, **b** via protonation and CC-coupling reaction sequence of the carbyne complexes **1a**, **b** with an ethereal solution of hydrogen chloride[6]. Similar compounds are formed by the carbonylation of $[MCl(CH_2SiMe_3)(PMe_3)]$ (M = Mo[7], W[8]) or by reacting the anion $[Mo(CO)_3\{HB(3,5\text{-}Me_2C_3HN_2)_3\}]^{\ominus}$ with aryldiazonium salts[9].



a, R = CH_3; **b**, R = p-$CH_3C_6H_4$

2a, **b** are orange-red, diamagnetic crystals, which are readily soluble in dichloromethane or acetone, but insoluble in diethyl ether and pentane. Their compositions and structures were determined by elemental analysis and by IR, ^{1}H-, and $^{13}C\{^1H\}$-NMR spectroscopy[10], as well as by X-ray structure analysis. On this basis, **2a** can be discribed as a pseudosquare pyramid in which the acyl ligand occupies a coordination site (Fig. 1). Its η^2-coordination follows from the W–C3 distance of 199.9(8) pm, which is shorter than a W–C single bond, and from the W–O3 bond length of 216.7(6) pm. At the same time, the C3–O3 double bond is lengthened. The geometry of the acyl-C3 deviates from that of an sp^2-hybridized carbon; the W–C3–O3 angle is similar to the corresponding angle in $[(CO)_2Cl(PMe)W(\eta^2\text{-}COCH_2SiMe_3)]_2$[8].

The acid-induced carbyne-acyl rearrangement is a novel reaction of transition metal-carbyne complexes; it confirms the nucleophilicity of the carbyne carbon atom in η^5-cyclopentadienyl-substituted carbyne complexes predicted by *Fenske* et al.[12]. A few examples are known for the probable first step in the reaction, leading to the as yet non-isolated carbene complex $(\eta^5\text{-}C_5H_5)(CO)_2ClW{=}CHR$ (R = CH_3, p-$CH_3C_6H_4$): protonation of $(PMe_3)_4ClW{\equiv}CH$[13], $CO(PPh_3)_2ClOs{\equiv}CR$[14], $(CO)_2[HB(C_3H_2N_2)_3]W{\equiv}C\text{–}SCH_3$[15] and $(\eta^5\text{-}C_5H_5)(CO)_2W{\equiv}C\text{–}NEt$[16].

A further reaction step could be protonation of this carbene complex followed by a formal CO insertion to give rise to **2**. An alternative mechanism might be a metal-induced, carbonyl-carbene coupling. The intermediate η^2-ketene complex could then undergo renewed addition of HCl to yield the η^2-acyl complex **2**.

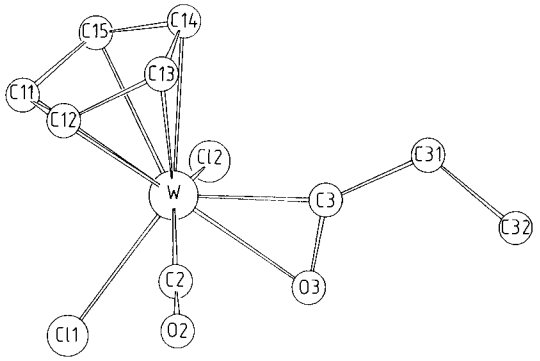


Fig. 1. Structure of **2a** in the crystal. Selected distances [pm] and angles [°]: W-Cl1 245.1(2), W-Cl2 247.5(2), W-C2 204.8(8), W-C3 199.9(8), W-O3 216.7(6), C3-O3 124.6(9), C3-C31 148.5(12), C2-O2 112.2(10), C31-C32 149.7(13); Cl1-W-Cl2 83.2(1), Cl1-W-C2 84.1(2), Cl1-W-O3 89.7(2), Cl1-W-C3 124.2(2), C2-W-C3 84.8(3), C3-W-O3 34.5(3), O3-C3-C31 125.8(7), W-C3-C31 154.0(6), W-C3-O3 80.2(5).

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[10] IR (ν(CO), CH_2Cl_2, [cm^{-1}]): **2a**: 2035; **2b**: 2038.—^{1}H-NMR (60 MHz, CD_2Cl_2, $CDHCl_2$ as rel. standard (δ = 5.40)): **2a**: δ = 5.70 (s, 5 H, C_5H_5), 3.53 (q, 2 H, CH_2), 1.48 (t, 3 H, CH_3).—**2b**: δ = 7.33 (s, 4 H, C_6H_4), 2.45 (s, 3 H, CH_3), 5.50 (s, 5 H, C_5H_5), 4.72 (s, 1 H), 4.68 (s, 1 H, CH_2). $^{13}C\text{-}\{^1H\}$-NMR (90 MHz, CD_2Cl_2, CD_2Cl_2 as rel. standard (δ = 54.2): **2b**: δ = 198.3 (W–CO), 277.9 (η^2-CO), 138.8, 130.5, 130.0, 129.5, 21.5 ($C_6H_4CH_3$), 95.4 (C_5H_5), 49.7 (CH_2).
[11] Orange crystals from dichloromethane (**2a**·CH_2Cl_2); monoclinic, C2/c, Z = 8, a = 2963.9(5), b = 741.1(1), c = 1346.3(2) pm; β = 105.01(1)°, T = −40°C; $Mo_{K\alpha}$ irradiation, graphite monochromator, ω-scan (0.9–29.3° min^{-1}, $2\theta_{max}$ = 51°). Of 2642 measured reflections, 2319 remain after Lorentz and polarization correction. Empirical absorption correction. Heavy atoms refined using Patterson methods, all non-H atoms refined anisotropically with full matrix (2135 observed reflections, 154 parameters, F_0 min = 35.0). H atoms, in part, found, in part calculated from ideal geometry. R_1 = 0.032, R_2 = 0.038. Further details on the crystal structure investigation can be obtained from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, by quoting the depository number CSD 50962, the names of the authors, and the journal citation.
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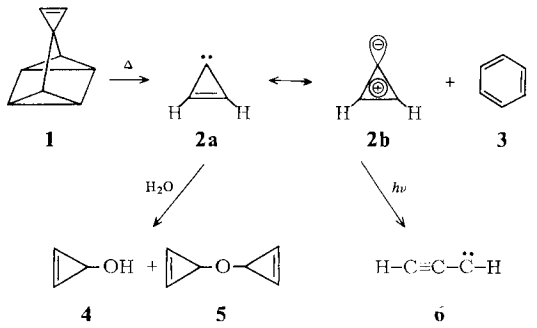
Cyclopropenylidene**

By *Hans Peter Reisenauer, Günther Maier*, Achim Riemann,* and *Reinhard W. Hoffmann**

Cyclopropenylidene **2a** ↔ **2b** is of considerable theoretical interest[1]. Until now, only the diphenyl[2] and bis(dialkylamino) derivatives[3] had been detected indirectly in trapping reactions. We report here the generation of cyclopropenylidene **2** by flash thermolysis and its matrix isolation.



The quadricyclane derivative **1**[4] was heated to 523 K under conditions of preparative vacuum flash pyrolysis at 1 torr. The products, which were trapped at 77 K, underwent exothermic polymerization upon thawing; in addition, benzene **3** was isolated in almost quantitative yield. If water was not completely excluded from the reaction, cyclopropenol **4** and dicyclopropenyl ether **5** were formed[5]. This indicates that in the pyrolysis of **1** a C_3H_2-fragment having an intact cyclopropene ring is cleaved off.

If the product of the pyrolysis is condensed with a large excess of argon[6] onto a window at 10 K immediately after it leaves the hot zone, the IR spectrum shows, apart from the bands from benzene, four additional absorptions (Table 1). Within the normal variations of calculations of this type (the calculated frequencies are ca. 10% too high), the frequencies and relative intensities are consistent with those of the four most intense IR bands predicted for **2**[1a]. Four other bands are too weak to be observed under our experimental conditions.

Table 1. Experimental and calculated [1a] IR spectrum of cyclopropenylidene **2**.

Band frequencies [cm^{-1}]		Rel. intensities	
Found	Calc.	Found	Calc.
—	3457	—	0.006
—	3418	—	0.012
—	1759	—	0.004
1279	1419	1.0	1.000
1063	1191	0.16	0.321
—	1071	—	inactive
—	998	—	0.031
888	983	0.33	0.309
789	854	0.34	0.395

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[**] Small Rings, Part 51. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.—Part 50: G. Maier, K. Euler, H. Irngartinger, M. Nixdorf, *Chem. Ber.*, in press.

The presence of cyclopropenylidene **2** is confirmed by the following experiment: Upon irradiation ($\lambda > 360$ nm) of the matrix-isolated pyrolysis product of **1**, only the four IR bands belonging to **2** disappear. Simultaneously, new absorptions at 3390, 3366, 412, 405, 261, and 248 cm^{-1} appear, whose frequencies correspond to the known values for matrix-isolated propynylidene **6**[7].

The photolytic conversion of **2** into **6** can also be observed using ESR spectroscopy. In accord with the singlet ground-state of **2**[1], the ESR spectrum of the matrix-isolated product of pyrolysis exhibits no triplet signal. After irradiation, the known spectrum[8] of the triplet carbene **6** is obtained, consistent with the results of IR studies.

2 does not react when the matrix is tempered for several hours at 35—40 K. After evaporation of the argon, a brown, polymeric residue remains. Evidence for the formation of the interesting dimer of **2**, 1,1-bicyclopropenylidene, could not be obtained.

Summary: Cyclopropenylidene **2** is stable in an argon matrix at 10 K and has, as predicted[1], a singlet ground-state.

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[5] **4** and **5** polymerize above 243 K, and, hence, only NMR data (203 K, [D_6]acetone) could be obtained. **4**: ^{1}H-NMR: $\delta = 7.91$ (d, 2H, $J = 1.5$ Hz), 3.76 (t, 1H, $J = 1.5$ Hz), 3.35 (1H); ^{13}C-NMR: $\delta = 120.8$ (d, J(C–H) = 227 Hz), 43.9 (d, J(C–H) = 200 Hz). **5**: ^{1}H-NMR: $\delta = 7.86$ (d, 4H, $J = 1.6$ Hz), 3.89 (t, 2H, $J = 1.6$ Hz); ^{13}C-NMR: $\delta = 128.6$ (d, J(C–H) = 224 Hz), 48.7 (d, J/C–H) = 200 Hz).

[6] Pyrolysis oven (G. Maier, G. Mihm, H. P. Reisenauer, *Chem. Ber. 115* (1982) 801) flanged directly onto the vacuum shroud of the cryostat (Displex Closed Cycle Refrigerations System CSA 202, Air Products). **1** was cooled to 223 K in a flask attached directly to the pyrolysis tube (10^{-4}–10^{-5} torr), pyrolyzed at 820—920 K within 5 h, and condensed with a large excess of argon onto the CsI window (10 K, distance from end to the hot zone ca. 5 cm).

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Direct Photochemical Cleavage of the Cyclobutane Ring in Bicyclo[4.2.0]octane on 185nm Irradiation in Solution**

By *Waldemar Adam** and *Thomas Oppenländer*

By analogy to cyclopropanes, which recently have been shown to exhibit interesting and diversified photochemistry on 185 nm irradiation in solution[1], cyclobutanes are

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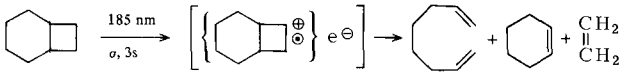
also expected to be photoactive in the far UV region since they possess appreciable absorption below 200 nm ($\sigma^* \leftarrow \sigma$ and Rydberg excitations)[2]. Cyclobutane rings can be cleaved efficiently by photochemical electron transfer with quinones as electron acceptors[3]. This photo-cleavage, which involves radical cation intermediates, plays a central role for the dissociation of thymine dimers in photodamaged DNA by photo-repairing enzymes[4]. Since $\sigma^* \leftarrow \sigma$-Rydberg excitation does lead to intermediates with radical cation character[2], it appeared important to explore the possibility of promoting direct photochemical cleavage of cyclobutanes that are devoid of chromophoric substituents by means of 185 nm irradiation in solution. That this cleavage indeed occurs is demonstrated using bicyclo[4.2.0]octane **1** as example.



1 **2**

Irradiation of a 0.044 M solution of **1** in *n*-pentane with the full output of a mercury low-pressure lamp (Gräntzel, Karlsruhe) affords 1,7-octadiene, cyclohexene, and ethylene. These photo-products were identified by co-injecting authentic materials onto three different capillary GC columns (86 m polypropylene glycol, 50 m OV-101, and 50 m Carbowax 20 M). In addition, 1,7-octadiene and cyclohexene were identified by their characteristic fragmentation patterns on capillary GC/MS analysis. Finally, 1,7-octadiene was collected by preparative gas chromatography (packed glass column 1.5 m × 8 mm, 10% β,β′-oxydipropionitrile on Chromosorb WHP, 100/200), and its 90 MHz ^{1}H-NMR spectrum found to be identical to that of an authentic sample.

Control experiments revealed that not even traces of cyclooctene were produced in the 185 nm photolysis, and at 254 nm (the major output of the mercury low-pressure lamp) **1** was completely photo-stable. Quantitative capillary GC analysis (50 m SE 30) gave a relative product composition of 1,7-octadiene: cyclohexene = 70:30, with a mass balance of >98% during the first 40 min of 185 nm irradiation. The quantum yields determined using the (*Z,E*)-isomerization of cyclooctene as actinometer[5] were $\Phi_S = 0.12 \pm 0.01$ for substrate consumption and $\Phi_P = 0.10 \pm 0.01$ and $\Phi_P = 0.030 \pm 0.003$ for 1,7-octadiene and cyclohexene, respectively.

In comparison, vacuum flash pyrolysis of **1** (18 torr, distillation through a Quartz tube, 450 °C) led to a relative product composition of 1,7-octadiene : cyclohexene = 11 : 89[6]. Ethylene was also formed, but the amount was difficult to quantify.

There are no analogous photoreactions of **1** at higher wavelengths because this alkyl-substituted cyclobutane[7] has no UV absorption above 200 nm. Mercury-sensitized irradiation of cyclooctene at 254 nm leads to **1**, postulated to be formed via cyclization of the intermediate tetramethylene diradical 1,4-cyclooctanediyl[8]. The fact that cyclooctene is not formed in the 185 nm photolysis of **1** precludes this 1,4-diradical as reactive intermediate, at least in its ground state. For example, in the thermolysis of the azoalkane 7,8-diazabicyclo[4.2.2]dec-7-ene, in which a ground state 1,4-cyclooctanediyl intervenes, both **1** and cyclooctene are produced[9]. Finally, the fact that the vacuum flash pyrolysis of **1** leads mainly to cyclohexene and ethylene[6] is evidence against the involvement of the 1,4-cyclooctanediyl as preferred intermediate in the 185 nm photolysis of **1**.

Since cyclobutane rings are efficiently cleaved in the electron-transfer photolysis of thymine dimers with quinones via intermediary radical cations[3], we postulate that the observed cleavage of **1** into 1,7-octadiene and cyclohexene in the 185 nm photolysis proceeds via (σ,3s)-Rydberg excitation. Promotion of an electron into a 3s Rydberg molecular orbital generates a species **2** with radical cation character[11], which on cyclobutane ring-cleavage and electron demotion would be expected to afford the observed products. Orbital symmetry arguments[11] also suggest that such cleavage processes should be facile. The demonstration that cyclobutane rings can be directly cleaved by 185 nm excitation provides novel opportunities for mechanistic investigations.

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Formation of Phenanthrenequinone from Benzil: A Novel Reaction of Graphite-Potassium Intercalates

By *Dov Tamarkin, Daphna Benny*, and *Mordecai Rabinovitz**

Reactions of the highly ordered potassium-graphite intercalate C_8K have evoked recently much interest. Due to its structure it reacts in a different mode, as compared with non-intercalated dispersed potassium[1]. Recently, we reported that *vic*-dibromides undergo with C_8K a stereospecific debromination reaction, and ketones undergo a bimolecular reduction in high yields to the respective pinacols. It has been suggested that the "layer-edge mechanism" is responsible for the specific reactivity of this reagent[2]. According to this mechanism ketones which are linked to adjacent potassium atoms at the graphite layer edge, form radical anions. These radical anions can then undergo a C–C bond formation reaction at those carbons bearing high spin density[2b].

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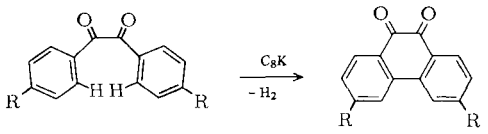

1, R = H
2, R = CH_3

3, R = H
4, R = CH_3

We now wish to report a novel reaction that α-diketones undergo with C_8K. Benzil **1** and *p,p'*-dimethylbenzil **2** with C_8K afford phenanthrenequinone **3** and 3,6-dimethylphenanthrenequinone **4**, respectively. This reaction involves an intramolecular carbon-carbon bond formation. The products are obtained in good yields and high purity, while experiments with dispersed potassium under similar conditions afforded only trace amounts of the respective quinone. Graphite-potassium intercalate C_8K is formed by heating to 200 °C potassium metal and dry graphite (B.D.H.) with magnetic stirring[3]. To freshly prepared C_8K (12.5 mmol in 20 mL dry THF), 2.5 mmol of benzil **1** (0.525 g, Fluka AG in 30 mL of THF) was added and stirred at room temperature (5 h, inert atmosphere). During this period of time hydrogen gas evolves. The red reaction mixture was quenched carefully with water and filtered, extracted with CH_2Cl_2 and evaporated. Phenanthrenequinone **3** (3.7 g, 70%, m.p. 208 °C(EtOH)[4] was obtained. Similarly, 3,6-dimethylphenanthrenequinone **4** was prepared from *p,p'*-dimethylbenzil in 72% yield (m.p. 216 °C/MeOH)[4]. The same reactions can also be performed in benzene or cyclohexane and the yields are 35% and 32%, respectively[5].

This novel C–C bond formation reaction provides a new synthetic pathway for the preparation of phenanthrenequinone-type compounds and their derivatives, especially in view of the easy affordability of substituted benzil derivatives from the corresponding benzaldehydes.

The evolution of the hydrogen gas was followed and measured. The rate of the gas evolution was found to be constant. This observation may indicate that the process is "layer-edge" controlled, i.e. the rate is determined by the surface area of the graphite lattice which contains ordered potassium atoms available for the reaction. This is consistent with the mechanism that we have previously described for the bimolecular reduction of ketones[2b]. The mechanistic behavior of C_8K reactions with ketones, diketones and their analogs is under further investigation.

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Acknowledgement: We thank Dr. *S. Zitrin* of the laboratories of the Israel Police Headquarters for CI MS measurements.

BOOK REVIEWS

Organotransition Metal Chemistry: Applications to Organic Synthesis. By *S. G. Davies*. Pergamon Press, Oxford 1982. x, 411 pp., bound, $ 85.00.

The use of transition metal complexes for the formation of carbon-carbon bonds is not in itself new; the classical investigations of *Roelen* and *Reppe* are nearly half a century old. Since then, however, the tremendous growth of organometallic chemistry has opened up a variety of reactions that have greatly augmented the armory of the synthetically oriented organic chemist.

The author of the present monograph has aimed at acquainting the organic synthesis-oriented reader with the possibilities of organometallic chemistry. The basic principles are dealt with in an introductory chapter, which, possibly because of space constraints, is so short that a list of references for further reading would have been appropriate. A review of the synthesis of various types of complexes and methods of ligand elimination follows a section concerned with the role of organometallic fragments as protective groups and as stabilizing functions. The central chapters deal with organometallic complexes as electrophilic and nucleophilic reaction partners; coupling and cyclization reactions, isomerization, redox and carbonylation reactions are also described. Each section is provided with a rich selection of literature examples. It is a pity that, nevertheless, such established reagents as organocopper compounds, which play such an important role in the formation of C–C bonds remain unmentioned—possibly because they are the subject of a recently published monograph by *G. Posner*. In addition to established catalytic processes, the main treatment is of stoichiometric reactions that are seen as a potential basis for new synthetic methods. The literature is covered up to mid-1980. The majority of the 700 references, which unfortunately are not without error, stems from the last five years.

The same theme has been the subject of several monographs lately. Nevertheless, this book by *Davies* is a welcome addition. It is clearly set out according to mechanistic principles and is thus of value as a primary reference source. It is well constructed from an instructional standpoint and gives a contemporary survey of the synthetic potentiality of organometallic chemistry. It will be of use to all those who seek an "organometallic" solution of their synthetic problems. Why this book, which is directly reproduced for the sake of topicality, is so expensive, is quite another question.

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Molecular Biology of the Cell. By *B. Alberts, D. Bray, J. Lewis, M. Raff, K. Roberts,* and *J. D. Watson*. Garland Publishing, New York 1983. xxxix, 1142 pp., bound, £ 33.95.

This textbook, which has been written by a group of authors, deals with only one subject, the cell, from various

points of view, thereby abandoning the usual compartmentation according to subject. The cell is the building block of all life. It is the host for subcellular life forms such as viruses and virus-like structures, it can also organize itself into a supracellular assemblage, losing some of its autonomy. A cell is not a temporal or structural continuum, but distinguishes itself by its functional complexity and its ability to adapt to its surroundings. Differentiation can be genetically programmed; it can, however, also be a response to environmental influences.

The first chapter of the book deals with the basic principles of cytology, by leading the reader from simple biomolecules up to multicellular organisms. The following section explains the techniques by which cellular structure and functions are currently investigated. Even complicated techniques such as cell fusion, the production of monoclonal antibodies, DNA cloning and cell sorting are explained in a very clear, albeit simplified, manner. The following chapter deals with the compartmentation of cells, cell growth and cell division and with cellular communication. The last chapter is even more topical than its predecessors. This covers the topics of heredity, fertilization and of cellular differentiation using the immune and nervous systems as examples and last of all the molecular biology of plants.

The individual contributions are written by specialists, who quote material published in their field up to about the end of 1982. The good didactic presentation and the courage to simplify are worthy of mention. Every contribution has been checked by a second expert for its factual content and comprehensibility. Each section ends with a summary and short list of literature references.

The quality of the illustrations is superior even to that of the text; for example, simplified schematic drawings are almost always placed alongside electron micrographs. The illustrations are not squeezed into the text on the principle of maximum utilization of space but each individual page is suitably graphically laid out even taking superscripts and subscripts into account.

Which readership is this book suitable for? It is to be recommended to each and every scientist in the fields of education, biology, chemistry and medicine who wishes to refresh and bring up-to-date his knowledge of cellular biology.

It is only suitable for students of biology or chemistry after they have completed the first part of their undergraduate courses, since the biological facts in the text and illustrations are somewhat schematized. Since the quantitative chemical-mechanistic aspect is neglected, the dominance of the illustrations leads to an overemphasis of static structures.

All in all an excellent book, that is currently unsurpassed in content and production.

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Advances in Polymer Science. Series editors: *H.-J. Cantow, G. Dall'Asta, K. Dušek, J. D. Ferry, H. Fujita, M. Gordon, G. Henrici-Olivé, H. H. Kausch, J. P. Kennedy, W. Kern, S. Okamura, S. Olivé, C. G. Overberger, T. Saegusa, G. V. Schulz, W.-P. Slichter,* and *J. K. Stille.* Springer-Verlag, Berlin. **Vol. 54: Spectroscopy: NMR, Fluorescence, FR-IR.** 1984. xi, 166 pp., bound, DM 98.00.—ISBN 3-540-12591-4; **Vol. 55: Solar Energy—Phase Transfer Catalysis—Transport Processes.** 1984. xi, 163 pp., bound, DM 98.00.—ISBN 3-540-12592-2; **Vol. 56: Anionic Polymerization.** 1984. xi, 143 pp., bound, DM 98.00.—ISBN 3-540-12792-5; **Vol. 57: Polymers in Medicine.** 1984. xi, 168 pp., bound, DM 108.00.—ISBN 3-540-12796-8

Specialist Periodical Reports. Amino Acids, Peptides and Proteins. Vol. 14. A Review of the Literature Published during 1981. Edited by *J. H. Jones.* The Royal Society of Chemistry, London 1983. xxii, 478 pp., bound, £ 73.00 (price reduction for members of the Royal Society of Chemistry), total price for Vol. 1—14, £ 294.00.—ISBN 0-85186-124-5

Photoelectron Spectroscopy. 2nd Edit. By *J. H. D. Eland.* Butterworths, London 1983. 271 pp., bound, £ 25.00.—ISBN 0-408-71057-8

Specialist Periodical Reports. General and Synthetic Methods. Vol. 6. A Review of the Literature Published During 1981. Edited by *G. Pattenden.* The Royal Society of Chemistry, London 1983. xiii, 416 pp., bound, £ 75.00 (price reduction for members of the Royal Society of Chemistry), total price for Vol. 2—6: £ 190.50.—ISBN 0-85186-874-6

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Experimental and Theoretical Nuclear Astrophysics; The Quest for the Origin of the Elements (Nobel Lecture)**

By William A. Fowler*

Ad astra per aspera et per ludum

I. Introduction

We live on planet Earth warmed by the rays of a nearby star we call the Sun. The energy in those rays of sunlight comes initially from the nuclear fusion of hydrogen into helium, deep in the solar interior. *Eddington* told us this in 1920, and in 1939 *Hans Bethe* developed the detailed nuclear processes involved in the fusion. For this he was awarded the Nobel Prize in Physics in 1967.

All life on earth, including our own, depends on sunlight and thus on nuclear processes in the solar interior. But the sun did not produce the chemical elements which are found in the earth and in our bodies. The first two elements and their stable isotopes, hydrogen and helium, emerged from the first few minutes of the early high-temperature, high-density stage of the expanding Universe, the so-called "big bang". A small amount of lithium, the third element in the periodic table, was also produced in the big bang, but the remainder of the lithium and all of beryllium, element four, and boron, element five, are thought to have been produced by the spallation of still heavier elements by cosmic radiation in the interstellar medium between stars. These elements are, in general, very rare, in keeping with this explanation of their origin, as reviewed in detail by *Audouze* and *Reeves*[1].

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Where did the heavier elements originate? The generally accepted answer is that all of the heavier elements from carbon, element six, up to long-lived radioactive uranium, element ninety-two, were produced by nuclear processes in the interior of stars in our own Galaxy. The stars we see at the present time in what we call the *Milky Way* are located in a spiral arm of our Galaxy. In Sweden, it is called *Vinter Gatan*, the Winter Street. Our eyes see only a small fraction of the one hundred billion stars in the Galaxy. Astronomers use almost the full range of the electromagnetic spectrum and thus can observe many more Galactic stars and even individual stars in other galaxies.

The stars which synthesized the heavy elements in the solar system were formed or born, subsequently evolved or aged, and eventually ejected the ashes of their nuclear fires into the interstellar medium over the lifetime of the Galaxy *before* the solar system itself formed, four and one-half billion years ago.

The lifetime of the Galaxy is thought to be more than ten billion years but less than twenty billion years. In any case, the Galaxy is much older than the solar system. The ejection of the nuclear ashes or newly formed elements took place by slow mass-loss during the old age of the star, called the *giant* stage of stellar evolution, or during the relatively frequent outbursts which astronomers call *novae*, or during the final spectacular stellar explosions called *supernovae*. Supernovae can be considered to be the death of stars, but the white dwarfs, neutron stars, or black holes that they leave behind may represent a form of stellar purgatory.

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In any case, the sun, the earth, and all the other planets in the solar system condensed under gravitational and rotational forces from a gaseous solar nebula in the interstellar medium consisting of "big bang" hydrogen and helium mixed with the heavier elements synthesized in earlier generations of Galactic stars. All of this is illustrated in Figure 1.

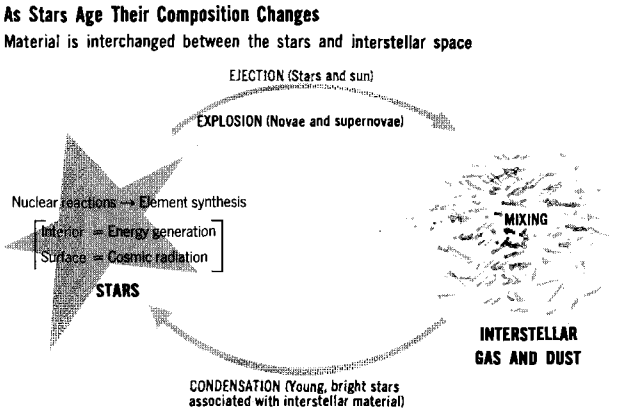

Fig. 1. Synthesis of the elements in stars.

The idea can be generalized to successive generations of stars in the Galaxy with the result that the heavy element content of the interstellar medium and the stars which form from it increase with time. The oldest stars in the Galactic halo, that is, those we believe to have formed first, are found to have heavy-element abundances less than one percent of the heavy-element abundance of the solar system; the oldest stars in the Galactic disk have approximately ten percent. Only the less massive stars among those first formed can have survived to the present as so-called Population II stars. Their small concentration of heavy elements may have been produced in a still earlier but more massive generation of stars, Population III, which rapidly exhausted their nuclear fuels and survived for only a very short lifetime. Stars formed in the disk of the Galaxy over its lifetime are referred to as Population I stars.

We speak of this element building as nucleosynthesis in stars. It can be generalized to other galaxies such as our twin, the Andromeda Nebula, and so this mechanism can be said to be a universal one. Astronomical observations on other galaxies have contributed much to our understanding of nucleosynthesis in stars.

We refer to the basic physics of energy generation and element synthesis in stars as Nuclear Astrophysics. It is a benign application of nuclear physics, in contrast to reactors and bombs. For the nuclear physicist, this contrast is a personal and professional paradox. However, there is one thing of which I am certain. The science which explains the origin of sunlight must not be used to raise a dust cloud which will black-out that sunlight from our planet.

As for all physics, the field of Nuclear Astrophysics involves experimental and theoretical activities on the part of its practitioners, and hence the first part of the title of this lecture. This lecture will emphasize nuclear experimental results and the theoretical analysis of those results almost, but not entirely, to the exclusion of other theoretical aspects. It will not in any way do justice to the observational activities of astronomers and cosmochemists, which are necessary to complete the cycle: experiment, theory, observation. Nor will it do justice to the calculations by many theoretical astrophysicists of the results of nucleosynthesis of the elements and their isotopes under astrophysical conditions during the many stages of stellar evolution.

My deepest personal interest is in experimental data, in the analysis of the data, and in the proper use of the data in theoretical stellar models. I continue to be encouraged in this regard by the one-hundred-and-and-ten-year-old quotation from *Mark Twain:*

There is something fascinating about science. One gets such wholesale returns of conjecture out of such a trifling investment of fact.

— Life on the Mississippi 1874

For me, *Twain*'s remark is a challenge to the experimentalist. The experimentalist must try to eliminate the word "trifling" through his endeavors in uncovering the facts of nature.

Experimental research and theoretical research are often very hard work. Fortunately, this is lightened by the fun of doing physics and in obtaining results which bring a personal feeling of intellectual satisfaction. To my mind, the hard work and the resulting intellectual fun transcend in a way the benefits which may accrue to society through subsequent technological applications. Please understand—I do not belittle these applications, but I am unable to overlook the fact that they are a two-edged sword. My subject matter resulted from the hard work of a nuclear astrophysicist, which when successful brought him joy and satisfaction. It was hard work, but it was fun. Thus, I have chosen as subtitle for this lecture—"*Ad astra per aspera et per ludum*", which can be freely translated "To the stars through hard work and fun." This is in keeping with my paraphrase of the biblical quotation from *Matthew* "Man shall not live by work alone".

With that in the record, let us next ask what are the goals of Nuclear Astrophysics? First of all, Nuclear Astrophysics attempts to understand energy generation in the sun and other stars at all stages of stellar evolution. Energy generation by nuclear processes requires the transmutation of nuclei into new nuclei with lower mass. The small decrease in mass is multiplied by the velocity of light squared, as *Einstein* taught us, and a relatively large amount of energy is released.

Thus, the first goal is closely related to the second goal that attempts to understand the nuclear processes which produced, under various astrophysical circumstances, the relative abundances of the elements and their isotopes in nature; whence the second part of the title of this lecture. Figure 2 shows a schematic curve of atomic abundances as a function of atomic weight. The data for this curve was first systemized from a plethora of terrestrial, meteoritic, solar and stellar data by *Hans Suess* and *Harold Urey*[2], and the available data has been periodically updated by

A. G. W. Cameron[3]. Major contributions to the experimental measurement of atomic transition rates needed to determine solar and stellar abundances have been made by my colleague, *Ward Whaling*[4]. References [3] and [4] occur in a monograph, Essays in Nuclear Astrophysics, which reviews the field up to 1982. In the words of one of America's baseball immortals, *Casey Stengel*, "You can always look it up".

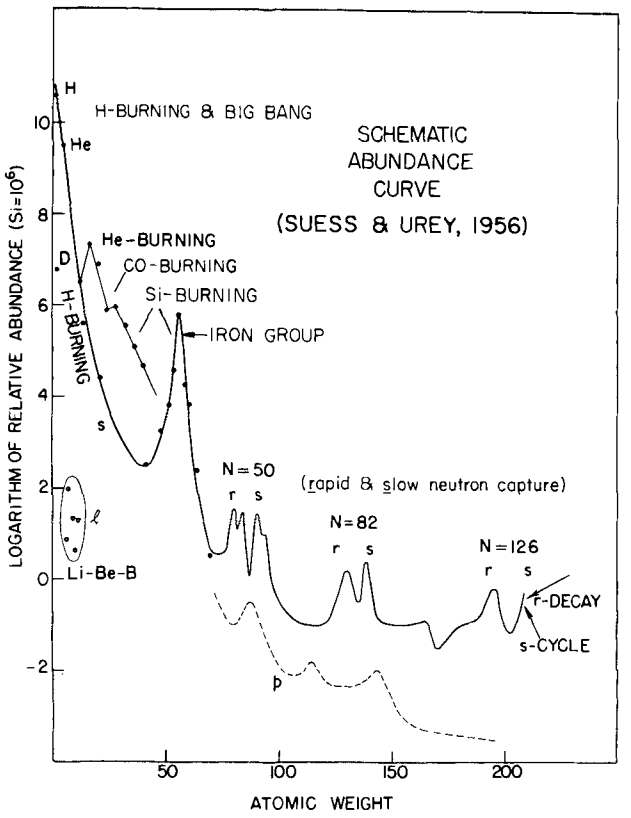

Fig. 2. Schematic curve of atomic abundances relative to $Si = 10^8$ versus atomic weight for the Sun and similar Main Sequence stars.

The curve in Figure 2 is frequently referred to as "universal" or "cosmic", but in reality it primarily represents relative atomic abundances in the solar system and in main sequence stars similar in mass and age to the sun. In current usage, the curve is described succinctly as "solar". It is beyond the scope of this lecture to elaborate on the difficult, beautiful research in astronomy and cosmochemistry which determined this curve. How this curve serves as a goal can be easily explained. In the sequel it will be noticed that calculations of atomic abundances produced under astronomical circumstances at various postulated stellar sites are almost invariably reduced to ratios relative to "solar" abundances.

II. Early Research on Element Synthesis

George Gamow and his collaborators, *R. A. Alpher* and *R. C. Herman*[5], attempted to synthesize all the elements during the big bang using a nonequilibrium theory involving neutron (n) capture with gamma-ray (γ) emission and electron (e) beta-decay by successively heavier nuclei. The synthesis proceeded in steps of one mass unit at a time, since the neutron has approximately unit mass on the mass scale used in all the physical sciences. As they emphasized, this theory meets grave difficulties beyond mass 4 (^{4}He) because no stable nuclei exist at atomic masses 5 and 8. *Enrico Fermi* and *Anthony Turkevich* attempted valiantly to bridge these "mass gaps" without success and permitted *Alpher* and *Herman* to publish the results of their attempts. Seventeen years later, *Wagoner, Fowler,* and *Hoyle*[6], armed with nuclear reaction data accumulated over the intervening years, succeeded only in producing ^{7}Li at a mass fraction of at most 10^{-8} compared to hydrogen plus helium for acceptable model universes. All heavier elements totaled less than 10^{-11} by mass. *Wagoner, Fowler,* and *Hoyle*[6] did succeed in producing ^{2}D, ^{3}He, ^{4}He, and ^{7}Li in amounts in reasonable agreement with observations at the time. More recent observations and calculations are frequently used to place constraints on models of the expanding universe and in general favor open models in which the expansion continues indefinitely.

It was in connection with the "mass gaps" that the W. K. Kellogg Radiation Laboratory first became involved, albeit unwittingly, in astrophysical and cosmological phenomena. Before proceeding, it is appropriate at this point to discuss briefly the origins of the Kellogg Radiation Laboratory, where I have worked for 50 years. The laboratory was designed and the construction supervised by *Charles Christian Lauritsen* in 1930 through 1931. *Robert Andrews Millikan*, the head of Caltech, acquired the necessary funds from *Will Keith Kellogg*, the American "cornflakes king". The Laboratory was built to study the physics of 1 MeV X-rays and the application of those X-rays in the treatment of cancer. In 1932, *Cockcroft* and *Walton* discovered that nuclei could be disintegrated by protons (p), the nuclei of the light hydrogen atom ^{1}H, accelerated to energies well under 1 MeV. *Lauritsen* immediately converted one of his X-ray tubes into a positive ion accelerator (they were powered by alternating current transformers!) and began research in nuclear physics. *Robert Oppenheimer* and *Richard Tolman* were instrumental in convincing *Millikan* that *Lauritsen* was doing the right thing. *Oppenheimer* played an active role in the theoretical interpretation of the experimental results obtained in the Kellogg Laboratory in the early crucial years.

Lauritsen supervised my doctoral research from 1933–1936, and I worked closely with him until his death. It was he who taught me that physics was both hard work and fun. He was a native of Denmark and was an accomplished violinist as well as physicist, architect, and engineer. He loved the works of *Carl Michael Bellman*, the famous Swedish poet-musician of the 18th century, and played and sang *Bellman* for his students. It is well known that many of *Bellman*'s work were drinking songs. That made it all the better.

We must now return to the first involvement of the Kellogg Radiation Laboratory in the mass gap at mass 5. In 1939, in Kellogg, *Hans Staub* and *William Stephens*[7] detected resonance scattering, by ^{4}He, of neutrons with orbital angular momentum equal to one in units of $\hbar$ (p-wave) and energy somewhat less than 1 MeV, as shown in Figure 3. This confirmed previous reaction studies by *Williams,*

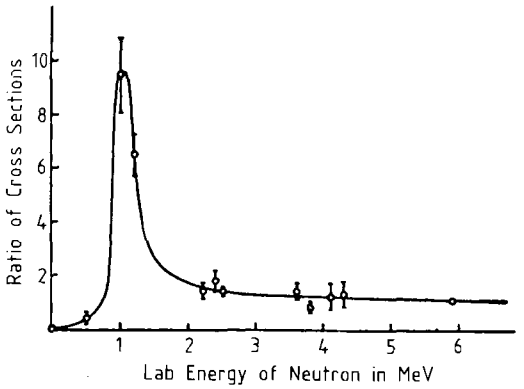

Fig. 3. The ratio of the backward scattering cross section of helium to hydrogen as a function of the laboratory energy of the incident neutron in MeV.

Shepherd, and *Haxby*[8] and showed that the ground state of ^{5}He is unstable. As fast as ^{5}He is made it disintegrates! The same was later shown to be true for ^{5}Li, the other candidate nucleus at mass 5. The Pauli exclusion principle dictates for fermions that the third neutron in ^{5}He must have at least unit angular momentum and not zero as permitted for the first two neutrons with antiparallel spins. The attractive nuclear force cannot match the outward centrifugal force in classical terminology. Still later, in the Kellogg Radiation Laboratory, *Tollestrup, Fowler,* and *Lauritsen*[9] confirmed, with improved precision, the discovery of *Hemmindinger*[10] that the ground state of ^{8}Be is unstable. They found the energy of the ^{8}Be break-up to be 89 ± 5 keV compared to the currently accepted value of 91.89 ± 0.05 keV! The Pauli exclusion principle is again at work in the instability of ^{8}Be. As fast as ^{8}Be is made it disintegrates into two ^{4}He-nuclei. The latter may be bosons but they consist of fermions. The mass gaps at 5 and 8 spelled the doom of *Gamow*'s hopes that all nuclear species would be produced in the big bang one unit of mass at a time.

The eventual commitment of the Kellogg Radiation Laboratory to Nuclear Astrophysics came about in 1939 when *Bethe*[11] brought forward the operation of the CN-cycle as one mode for the fusion of hydrogen into helium in stars (since oxygen has been found to be involved, the cycle is now known as the CNO-cycle). *Charles Lauritsen,* his son *Thomas Lauritsen,* and I were measuring the cross sections of the proton bombardment of the isotopes of carbon and nitrogen which constitute the CN-cycle. *Bethe*'s paper[11] told us that we were studying in the laboratory, processes which are occurring in the sun and other stars. It made a lasting impression on us. World War II intervened, but in 1946, on returning the laboratory to nuclear experimental research, *Lauritsen* decided to continue in low-energy, *classical* nuclear physics with emphasis on the study of nuclear reactions thought to take place in stars. In this, he was strongly supported by *Ira Bowen,* a Caltech Professor of Physics, who had just been appointed Director of the Mt. Wilson Observatory, by *Lee DuBridge,* the new President of Caltech, by *Carl Anderson,* Nobel Prize winner 1936, and by *Jesse Greenstein,* newly appointed to establish research in astronomy at Caltech. In Kellogg, *Lauritsen* did not follow the fashionable trend to higher and higher energies which has continued to this day. He did, however, support *Robert Bacher* and others in establishing high energy physics at Caltech.

Although *Bethe*[11], in 1939, and others, still earlier, had previously discussed energy generation by nuclear processes in stars, the grand concept of nucleosynthesis in stars came from *Fred Hoyle*[12]. In two classic papers, the basic ideas of the concept were presented within the framework of stellar structure and evolution with the use of the then known nuclear data.

Again, the Kellogg Laboratory played a role. Before his second paper, *Hoyle* was puzzled by the slow rate of the formation of ^{12}C-nuclei from the fusion ($3\alpha \rightarrow {}^{12}$C) of three alpha-particles (α) or ^{4}He-nuclei in Red Giant Stars. *Hoyle* was puzzled because his own work with *Schwarzschild*[13] and previous work of *Sandage* and *Schwarzschild*[14] had convinced him that helium burning through $3\alpha \rightarrow {}^{12}$C should commence in Red Giants just above 10^8 K rather than at 2×10^8 K, as required by the reaction rate calculation of *Salpeter*[15]. *Salpeter* made his calculation while a visitor at the Kellogg Laboratory during the summer of 1951 and used the Kellogg value[9] for the energy of ^{8}Be in excess of two ^{4}He to determine the resonant rate for the process ($2\alpha \leftrightarrow {}^8$Be), which takes into account both the formation and decay of the ^{8}Be. However, in calculating the next step, $^8\text{Be} + \alpha \rightarrow {}^{12}\text{C} + \gamma$, *Salpeter* had treated the radiative fusion as nonresonant.

Hoyle realized that this step would be speeded up by many orders of magnitude, thus reducing the temperatures for its onset, if there existed an excited state of ^{12}C with energy 0.3 MeV in excess of $^8\text{Be} + \alpha$ at rest and with the angular momentum and parity ($0^+, 1^-, 2^+, 3^-, \ldots$) dictated by the selection rules for these quantities. *Hoyle* came to the Kellogg Laboratory early in 1953 and questioned the staff about the possible existence of his proposed excited state. To make a long story short, *Ward Whaling* and his visiting associates and graduate students[16] decided to go into the laboratory and search for the state using the ^{14}N $(d,\alpha)^{12}$C reaction. They found it to be located almost exactly where *Hoyle* had predicted. It is now known to be at 7.654 MeV excitation in ^{12}C or 0.2875 MeV above $^8\text{Be} + \alpha$ and 0.3794 MeV above 3α. *Cook, Fowler, Lauritsen,* and *Lauritsen*[17] then produced the state in the decay of radioactive ^{12}B and showed that it could break up into 3α and thus, by reciprocity, could be formed from 3α. They argued that the spin and parity of the state must be 0^+, as is now known to be the case.

The $3\alpha \rightarrow {}^{12}$C fusion in Red Giants jumps the mass gaps at 5 and 8. This process could never occur under big bang conditions. By the time the ^{4}He was produced in the early expanding Universe, the subsequent density and temperature were too low for the helium fusion to carbon to occur. In contrast, in Red Giants, after hydrogen conversion to helium during the Main Sequence stage, gravitational contraction of the helium core raises the density and temperature to values where helium fusion is ignited. *Hoyle* and *Whaling* showed that conditions in Red Giant stars are just right.

Fusion processes can be referred to as nuclear burning in the same way we speak of chemical burning. Helium burning in Red Giants succeeds hydrogen burning in Main Sequence stars and is in turn succeeded by carbon, neon, oxygen, and silicon burning to reach to the elements near iron and somewhat beyond in the periodic table. With these nuclei of intermediate mass as seeds, subsequent processes similar to *Gamow*'s involving neutron capture at a slow rate (*s*-process) or at a rapid rate (*r*-process) continued the synthesis beyond ^{209}Bi, the last stable nucleus, up through short-lived radioactive nuclei to long-lived ^{232}Th, ^{235}U, and ^{238}U, the parents of the natural radioactive series. This last nucleus requires the *r*-process which actually builds beyond mass 238 to radioactive nuclei which decay back to ^{232}Th, ^{235}U, and ^{238}U rapidly at the cessation of the process.

The need for two neutron capture processes was provided by *Suess* and *Urey*[2]. With the adroit use of relative isotopic abundances for elements with several isotopes, they demonstrated the existence of the double peaks (*r* and *s*) in Figure 2. It was immediately clear that these peaks were associated with neutron shell filling at the magic neutron numbers $N=50$, 82, and 126 in the nuclear shell model of *Hans Jensen* and *Maria Goeppert-Mayer*, who won the Nobel Prize in Physics just twenty years ago.

In the *s*-process, the nuclei involved have low capture cross-sections at shell closure and thus large abundances to maintain the *s*-process flow. In the *r*-process, it is the proton-deficient radioactive progenitors of the stable nuclei which are involved. Low capture cross-sections and small beta-decay rates at shell closure lead to large abundances, but after subsequent radioactive decay these large abundances appear at lower A values than for the *s*-process, since Z is less and thus $A=N+Z$ is less. In *Hoyle*'s classic papers[12], stellar nucleosynthesis up to the iron group elements was attained by charged particle reactions. Rapidly rising Coulomb barriers for charged particles curtailed further synthesis. *Suess* and *Urey*[2] made the breakthrough which led to the extension of nucleosynthesis in stars by neutrons unhindered by Coulomb barriers all the way to ^{238}U.

The complete run of the synthesis of the elements in stars was incorporated into a paper by *Burbidge, Burbidge, Fowler,* and *Hoyle*[18], commonly referred to as B^{2}FH, and was independently developed by *Cameron*[19]. Notable contributions to the astronomical aspects of the problem were made by *Jesse Greenstein*[20] and by many other observational astronomers. Since that time, Nuclear Astrophysics has developed into a full-fledged scientific activity including the exciting discoveries of isotopic anomalies in meteorites by my colleagues *Gerald Wasserburg, Dimitri Papanastassiou,* and *Samuel Epstein* and many other cosmochemists. What follows will highlight a few of the many experiments and theoretical researches under way at the present time or carried out in the past few years. This account will emphasize research activities in the Kellogg Laboratory, because they are closest to my interest and knowledge. However, copious references to the work of other laboratories and institutions are cited in the hope that the reader will obtain a broad view of current experimental and theoretical studies in Nuclear Astrophysics.

This account cannot discuss the details of the nucleosynthesis of all the elements and their isotopes, which would, for a given nuclear species, involve discussing all the reactions producing that nucleus and all those which destroy it. The reader will find some of these details for ^{12}C, ^{16}O, and ^{55}Mn.

It will be noted that the measured cross-sections for the reactions are customarily very small at the lowest energies of measurement, for $^{12}C(\alpha,\gamma)^{16}O$ even less than one nanobarn (10^{-33} cm^2) near 1.4 MeV. This means that experimental Nuclear Astrophysics requires accelerators with large currents of well focussed, monoenergic ion beams, thin targets of high purity and stability, detectors of high sensitivity and energy resolution, and experimentalists with great tolerance for the long running-times required, and with patience in accumulating data of statistical significance. Classical Rutherfordian measurements of nuclear cross-sections are required in experimental nuclear astrophysics, and the results are in turn essential to our understanding of the physics of nuclei.

A comment on nuclear reaction notation is necessary at this point. In the reaction $^{12}C(\alpha,\gamma)^{16}O$ discussed in the previous paragraph, ^{12}C is the laboratory target nucleus, α is the incident nucleus (^{4}He) accelerated in the laboratory, γ is the photon produced and detected in the laboratory, and ^{16}O is the residual nucleus which can also be detected if it is desirable to do so. If ^{12}C is accelerated against a gas target of ^{4}He and the ^{16}O-products are detected but not the gamma rays, then the laboratory notation is $^4He(^{12}C,^{16}O)\gamma$. The stars could not care less. In stars, all the particles are moving and only the center-of-momentum system is important for the determination of stellar reaction rates. In $^{12}C(\alpha,n)^{15}O(e^+\nu)^{15}N$, n is the neutron promptly produced and detected and e^+ is the beta-delayed positron which can also be detected. The neutrino emitted with the positron is designated by ν.

As an aside at this point, I am proud to recall that I first spoke to the Royal Swedish Academy of Sciences on "Nuclear Reactions in Stars" on January 26, 1955. It does not seem so long ago, and some of you in the audience heard that talk!

III. Stellar Reaction Rates from Laboratory Cross Sections

Thermonuclear reaction rates in stars are customarily expressed as $N_A\langle\sigma v\rangle$ reactions per second per (mole cm^{-3}) where $N_A=6.022\times10^{23}$ mole^{-1} is Avogadro's number and $\langle\sigma v\rangle$ is the Maxwell-Boltzmann average as a function of temperature for the product of the reaction cross section, σ, in cm^2, and the relative velocity of the reactants, v in cm sec^{-1}. Multiplication of $\langle\sigma v\rangle$ by the product of the number densities per cm^3 of the two reactants is necessary to obtain rates in reactions per second per cm^3. N_A is incorporated so that mass fractions can be used, as described in detail by *Fowler, Caughlan,* and *Zimmerman*[21]. These authors also describe procedures for reactions involving more than two reactants and give analytical expressions for reactions mainly involving γ, e, n, p, and α with nuclei having atomic mass number $A\leq30$. Bose-Einstein statistics

for γ have been necessarily incorporated, but the extension to Fermi-Dirac statistics for degenerate e, n, and p and the extension to Bose-Einstein statistics for α are not included. Factors for calculating reverse reaction rates are given.

Early work on the evaluation of stellar reaction rates from experimental laboratory cross sections was reviewed in *Bethe*'s Nobel Lecture[11]. *Fowler, Caughlan,* and *Zimmerman*[21] have provided detailed numerical and analytical procedures for converting laboratory cross sections into stellar reaction rates. It is first of all necessary to accommodate the rapid variation of the nuclear cross sections at low energies, which are relevant in astrophysical circumstances. For neutron-induced reactions this is accomplished by defining a cross section S-factor equal to the cross section (σ) multiplied by the interaction velocity (v) in order to eliminate the usual v^{-1} singularity in the cross section at low velocities and low energies.

For reactions induced by charged particles such as protons, alpha particles, or the heavier ^{12}C, ^{16}O ... nuclei, it is necessary to accommodate the decrease by many orders of magnitude from the lowest laboratory measurements to the energies of astrophysical relevance. This is done in the way first suggested by *E. E. Salpeter*[22] and emphasized by *Bethe* in 1967[11].

Table 1. Definition of the S-Factor (*Bethe* 1967 [11]) as a function of reaction energy E.

$\sigma(E) = \pi\lambda^2 \times P \times$ intrinsic nuclear factor
$\pi\lambda^2 \propto E^{-1}$ (λ = de Broglie wavelength/2π
$P(E)$ = Gamow penetration factor
$\propto \exp(-E_G^{1/2}/E^{1/2})$; $E_G \approx Z_0^2 Z_1^2 A$ [MeV]
$\Rightarrow S(E) \equiv E\sigma(E)\exp(+E_G^{1/2}/E^{1/2})$
$S(E)$ { permits more precise extrapolation from lowest energy measurements in laboratory to very low effective stellar energies

Table 1 shows how a relatively slowly varying S-factor can be defined by eliminating the rapidly varying term in the Gamow penetration factor governing transmission through the Coulomb barrier. The cross section is usually expressed in barns (10^{-24} cm^2) and the energy in MeV (1.602×10^{-6} erg), so that the S-factor is expressed in MeV-barns, although keV-barns is sometimes used. In Table 1 the two charge numbers and the reduced mass in atomic mass units of the interacting nuclei are designated by Z_0, Z_1, and A. Table 2 then shows how stellar reaction rates can be calculated as an average over the Maxwell-Boltzmann distribution for both nonresonant and resonant cross sections. In Table 2 the effective stellar reaction energy is given numerically by $E_0 = 0.122(Z_0^2 Z_1^2 A)^{1/3} T_9^{2/3}$ MeV, where T_9 is the temperature in units of 10^9 K. Expressions for reaction rates derived from theoretical statistical model calculations are given by *Woosley, Fowler, Holmes,* and *Zimmerman*[23].

It is true that the extrapolation from the cross sections measured at the lowest laboratory energies to the cross sections at the effective stellar energy can often involve a decrease of many orders of magnitude. However, the elimination of the Gamov penetration factor, which causes this decrease, is based on the solution of the Schroedinger equation for the Coulomb wave functions in which one can have considerable confidence. The main uncertainty lies in the variation of the S-factor with energy, which depends primarily on the value chosen for the radius at which formation of a compound nucleus between two interacting nuclei or nucleons occurs, as discussed long ago in [18]. The radii used by my colleagues and I in recent work are given in [23]. There is, in addition, the uncertainty in the *intrinsic nuclear factor* of Table 1, which can only be eliminated by recourse to laboratory experiments. The effect of a resonance in the compound nucleus just below or just above the threshold for a given reaction can often be ascertained by determination of the properties of the resonance in other reactions in which it is involved and which are easier to study.

Table 2. Stellar reaction rates as functions of temperature (T).

$\langle\sigma v\rangle_{MB} = f(T) \propto T^{-3/2} \int S(E) \exp(-E_G^{1/2}/E_{1/2} - E/kT)\,dE$
MB ≡ average over Maxwell-Boltzmann distribution maximum in integrand occurs at E_r and at
E_0 ≡ effective stellar reaction energy $\propto E_G^{1/3} T^{2/3}$

Nonresonant rate
$\langle\sigma v\rangle_{nr} \propto S(E_0) T^{-2/3} \exp(-3E_0/kT)$; $E_0/kT \propto T^{-1/3}$

Resonant rate
$\langle\sigma v\rangle_r \propto S(E_r) T^{-3/2} \exp(-E_r/kT)$
E_r = energy at resonance

IV. Hydrogen Burning in Main Sequence Stars and the Solar Neutrino Problem

Hydrogen burning in Main Sequence stars has contributed at the present time only about 20 percent more helium than that which resulted from the big bang. However, hydrogen burning in the sun has posed a problem for many years. In 1938, *Bethe* and *Critchfield*[24] proposed the proton-proton or *pp*-chain as one mechanism for hydrogen burning in stars. From many cross section measurements at Kellogg and elsewhere, it is now known to be this mechanism, rather than the CNO-cycle, which operates in the sun.

Our knowledge of the weak nuclear interaction (beta decay, neutrino emission, and absorption, etc.) tells us that two neutrinos are emitted when four hydrogen nuclei are converted into helium nuclei. Detailed elaboration of the pp-chain by *Fowler*[25] and *Cameron*[26] showed that a small fraction of these neutrinos, those from the decay of ^7Be and ^8B, should be energetic enough to be detectable through interaction with the ^{37}Cl nucleus to form radioactive ^{37}Ar, a method of neutrino detection suggested by *Pontecorvo*[27] and *Alvarez*[28]. *Raymond Davis* and his collaborators[29] have attempted for more than 25 years to detect these energetic neutrinos employing a 380000 L tank of perchloroethylene ($C_2{}^{35}Cl_3{}^{37}Cl_1$) located one mile deep in the Homestake Gold Mine in Lead, South Dakota. They find only about one quarter of the number expected on the basis of the model-dependent calculations of *Bahcall* et al.[30].

Something is wrong — either the standard solar models are incorrect, the relevant nuclear cross sections are in error, or the electron-type neutrinos produced in the sun are converted in part into undetectable muon neutrinos or taon neutrinos on the way from the sun to the earth. There have indeed been controversies about the nuclear cross sections, which for the most part, however, have been resolved, as reviewed in *Robertson* et al., *Osborne* et al.[31], and *Skelton* and *Kavanagh*[32].

It is generally agreed that the next step is to build a detector which will detect the much larger flux of low energy neutrinos from the sun through neutrino absorption by the nucleus ^{71}Ga to form radioactive ^{71}Ge. This will require 30 to 50 tons of gallium at a cost (for 50 tons) of approximately 25 million dollars. An international effort is being made to obtain the necessary amount of gallium. We are back at square one in Nuclear Astrophysics. Until the solar neutrino problem is resolved, the basic principles underlying the operation of nuclear processes in stars are in question. A gallium detector should go a long way toward resolving the problem.

The chlorine detector must be maintained in low level operation until the chlorine and gallium detectors can be operated at full level simultaneously. Otherwise, endless conjecture concerning time variations in the solar neutrino flux will ensue. Moreover, the results of the gallium observations may uncover information that has been overlooked in the past chlorine observations.

The CNO-cycle operates at the higher temperatures which occur during hydrogen burning in Main Sequence stars somewhat more massive than the sun. This is the case, because the CNO-cycle reaction rates rise more rapidly with temperature than those of the *pp*-chain. The cycle is important because ^{13}C, ^{14}N, ^{15}N, ^{17}O, and ^{18}O are produced from ^{12}C and ^{16}O as seeds. The role of these nuclei as sources of neutrons during helium burning is discussed in Section V.

V. The Synthesis of ^{12}C and ^{16}O and Neutron Production in Helium Burning

The human body is 65% by mass oxygen and 18% carbon, with the remainder mostly hydrogen. Oxygen (0.85%) and carbon (0.39%) are the most abundant elements heavier than helium in the Sun and similar Main Sequence stars. It is little wonder that the determination of the ratio ^{12}C/^{16}O produced in helium burning is a problem of paramount importance in Nuclear Astrophysics. This ratio depends in a fairly complicated manner on the density, temperature, and duration of helium burning, but depends directly on the relative rates of the $3\alpha \rightarrow {}^{12}$C process and the ^{12}C$(\alpha,\gamma)^{16}$O process. If $3\alpha \rightarrow {}^{12}$C is much faster than ^{12}C$(\alpha,\gamma)^{16}$O, no ^{16}O is produced in helium burning. If the reverse is true, no ^{12}C is produced. For the most part, the subsequent reaction ^{16}O$(\alpha,\gamma)^{20}$Ne is slow enough to be neglected.

There is general agreement about the rate of the $3\alpha \rightarrow {}^{12}$C process, as reviewed by *Barnes*[33]. However, there is a lively controversy at the present time about the laboratory cross section for ^{12}C$(\alpha,\gamma)^{16}$O and about its theoretical extrapolation to the low energies at which the reaction effectively operates. The situation is depicted in Figures 4, 5, and 6, taken with some modification from *Laganke* and *Koonin*[34], *Dyer* and *Barnes*[35], and *Kettner* et al.[36]. The Caltech data obtained at the Kellogg Laboratory is shown as the experimental points in Figure 4, taken from *Dyer* and *Barnes*[35], who compared their results with theoretical calculations by *Koonin, Tombrello,* and *Fox*[35]. The Münster data are shown as the experimental points in Figure 5, taken from *Kettner* et al.[36], in comparison with the data of *Dyer* and *Barnes*[35]. The theoretical curves which yield the best fit to the two sets of data are those of *Laganke* and *Koonin*[34].

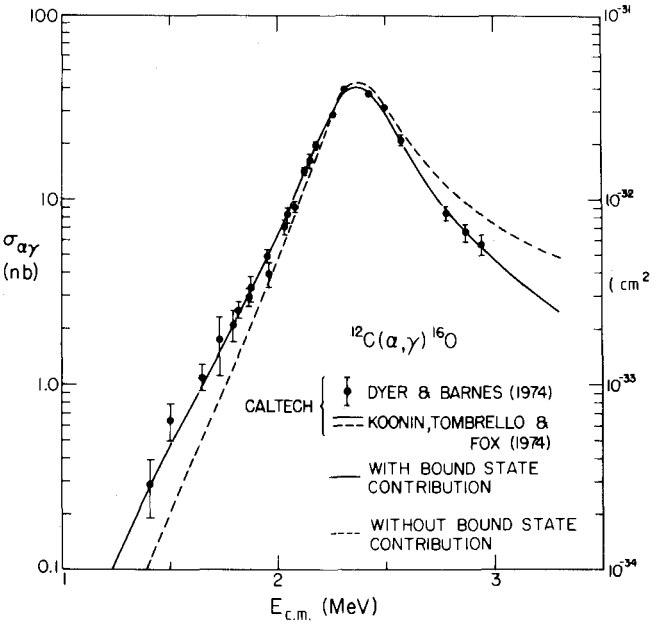

Fig. 4. The cross section σ in nanobarns (nb) versus center-of-momentum energy in MeV for ^{12}C$(\alpha,\gamma)^{16}$O, measured by *Dyer* and *Barnes* [35] and compared with theoretical calculations by *Koonin, Tombrello,* and *Fox* (see [35]).

The crux of the situation is made evident in Figure 6, which shows the extrapolations of the Caltech and Münster cross section factors from the lowest measured laboratory energies (≈ 1.4 MeV) to the effective energy ≈ 0.3 MeV, at $T = 1.8 \times 10^8$ K, a representative temperature for helium burning in Red Giant stars. The extrapolation in cross sections covers a range of 10^{-8}! The rise in the cross section factor is due to the contributions of two bound states in the ^{16}O nucleus just below the ^{12}C$(\alpha,\gamma)^{16}$O threshold, as clearly indicated in Figure 4. It is these contributions plus differences in the laboratory data which produce the current uncertainty in the extrapolated *S*-factor. Note that *Laganke* and *Koonin*[34] increase the 1975 extrapolation of the Caltech data by *Fowler, Caughlan,* and *Zimmerman*[21] by a factor of 2.7 and lower the 1982 extrapolation of the Münster data by 23%. There remains a factor of 1.6 between their extrapolation of the Münster data and of the Caltech data. There is a lesson in all of this. The semiempirical extrapolation of their data by the experimentalists *Dyer* and *Barnes*[35] was only 30% lower than that of *Laganke* and *Koonin*[34] and their quoted uncertainty ex-

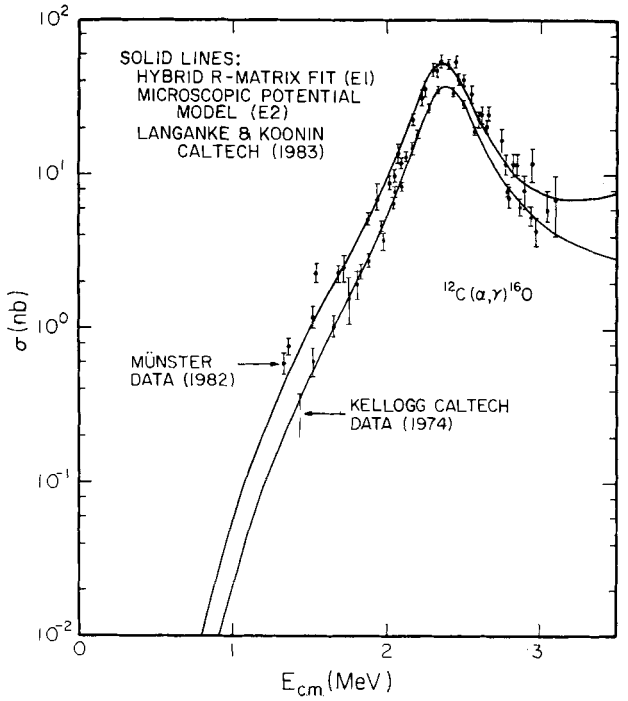

Fig. 5. The cross section σ in nanobarns (nb) versus center-of-momentum energy in MeV for $^{12}C(\alpha,\gamma)^{16}O$. The Münster data was obtained by *Kettner* et al. [36] and the Kellogg Caltech data, by *Dyer* und *Barnes* [35]. The solid lines are theoretical calculations made by *Laganke* and *Koonin* [34].

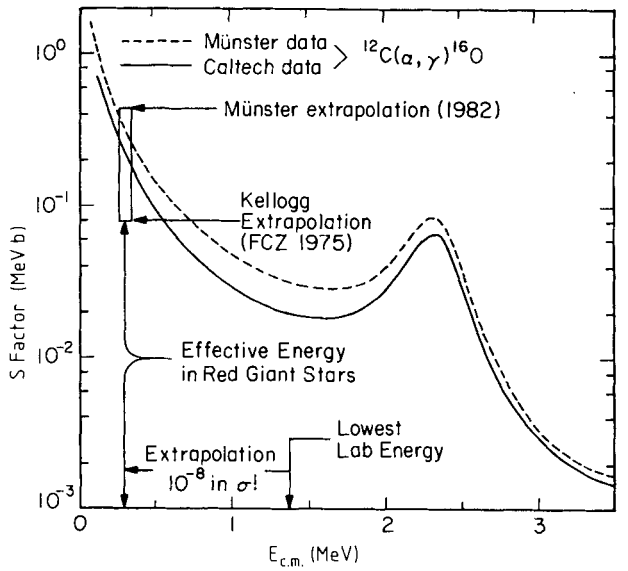

Fig. 6. The cross section factor S in MeVb versus center-of-momentum energy in MeV for $^{12}C(\alpha,\gamma)^{16}O$. The dashed and solid curves are the theoretical extrapolations of the Münster and Kellogg Caltech data by *Laganke* and *Koonin*, respectively [34].

tended to the value of *Laganke* and *Koonin*[34]. *Caughlan* et al.[21] will tabulate the analysis of the Caltech data by *Laganke* and *Koonin*[34].

With so much riding on the outcome, it will come as no surprise that both laboratories are engaged in extending their measurements to lower energies with higher precision. In the discussion of quasistatic silicon burning in what follows, it will be found that the abundances produced in that stage of nucleosynthesis depend, in part, on the ratio of ^{12}C to ^{16}O produced in helium burning, and that the different extrapolations shown in Figure 6 are in the range crucial to the ultimate outcome of silicon burning. These remarks do not apply to explosive nucleosynthesis.

Recently, the ratio of ^{12}C to ^{16}O produced under the special conditions of helium flashes during the asymptotic giant phase of stellar evolution has become of great interest. The hot blue star PG 1159-035 has been found to undergo nonradial pulsations with periods of 460 and 540 seconds and others not yet accurately determined. The star is obviously highly evolved, having lost its hydrogen atmosphere and leaving only a hot-dwarf of about 0.6 solar masses behind. Theoretical analysis of the pulsations by *Starrfield* et al. and *Becker*[37] requires substantial amounts of oxygen in the pulsation-driving regions where the oxygen is alternately ionized and deionized. Carbon is completely ionized in these regions and only diminishes the pulsation amplitude. It is not yet clear that sufficient oxygen is produced in helium flashes, which certainly involve $3\alpha \rightarrow {}^{12}C$, but may not last long enough for $^{12}C(\alpha,\gamma)^{16}O$ to be involved. The problem may not lie in the nuclear reaction rates according to [37]. We shall see!

In what follows in this paper, β^+-decay is designated by $(e^+\nu)$ since both a positron (e^+) and a neutrino (ν) are *emitted*. Similarly, β^--decay is designated by $(e^-\bar{\nu})$ since both an electron (e^-) and antineutrino $(\bar{\nu})$ are *emitted*. Electron capture (often indicated by ε) is designated by (e^-,ν), the comma indicating that an electron is captured and a neutrino emitted. The notations $(e^+,\bar{\nu})$, (ν,e^-) and $(\bar{\nu},e^+)$ should now be obvious.

Neutrons are produced when helium burning occurs under circumstances in which the CNO-cycle has been operative in the previous hydrogen burning. When the cycle does not go to completion, copious quantities of ^{13}C are produced in the sequence of nuclear reactions $^{12}C(p,\gamma)^{13}N(e^+\nu)^{13}C$. In subsequent helium burning, neutrons are produced by $^{13}C(\alpha,n)^{16}O$. When the cycle goes to completion, the main product (>95%) is ^{14}N. In subsequent helium burning, ^{18}O and ^{22}Ne are produced in the sequence of reactions $^{14}N(\alpha,\gamma)^{18}F(e^+\nu)^{18}O(\alpha,\gamma)^{22}Ne$, and these nuclei in turn produce neutrons through $^{18}O(\alpha,n)^{21}Ne(\alpha,n)^{24}Mg$ and $^{22}Ne(\alpha,n)^{25}Mg$. However, the astrophysical circumstances and sites under which the neutrons produce heavy elements through the *s*-process and the *r*-process are, even today, matters of some controversy and much study (see Section XI).

VI. Carbon, Neon, Oxygen, and Silicon Burning

The advanced burning processes discussed in this section involve the network of reactions shown in Figure 7. Because of the high temperature at which this network can operate, radioactive nuclei can live long enough to serve as live reaction targets. In addition, excited states of even the stable nuclei are populated and also serve as targets. The determination of the nuclear cross sections and stellar rates of the approximately 1000 reactions in the network has involved and will continue to involve extensive experimental and theoretical effort.

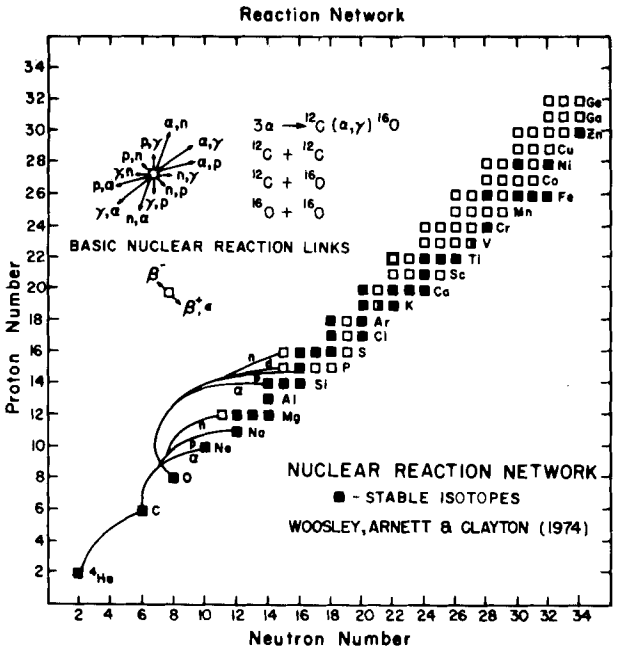

Fig. 7. The reaction network for nucleosynthesis involving the most important stable and radioactive nuclei with $N=2$ to 34 and $Z=2$ to 32. Stable nuclei are indicated by solid squares. Radioactive nuclei are indicated by open squares.

The following discussion applies to stars so massive enough that electron degeneracy does not set in as nuclear evolution proceeds through the various burning stages mentioned in this section. In less massive stars, electron degeneracy can terminate further nuclear evolution at certain stages, with catastrophic results leading to the disruption of the stellar system. The reader will find Figure 8, especially Figure 8a, instructive in following the discussion in this section. Figure 8 is taken from *Woosley* and *Weaver*[38], and a much more detailed recent version is shown in Figure 9, from *Weaver, Woosley,* and *Fuller*[39]. Figure 8a applies to the preexplosive stage of a young (Population I) star of 25 solar masses and shows the result of various nuclear burnings in the following mass zones: 1) $>10\,M_\odot$, convective envelope with the results of some CNO-burning; 2) $7-10\,M_\odot$, products mainly of H-burning; 3) $6.5-7\,M_\odot$, products of He-burning; 4) $1.9-6.5\,M_\odot$ products of C-burning; 5) $1.8-1.9\,M_\odot$, products of Ne-burning; 6) $1.5-1.8\,M_\odot$, products of O-burning; 7) $<1.5\,M_\odot$, the products of Si-burning in the partially neutronized core are not shown in detail but consist mainly of ^{54}Fe as well as substantial amounts of other neutron-rich nuclei such as ^{48}Ca, ^{50}Ti, ^{54}Cr and ^{58}Fe. ^{54}Fe, ^{48}Ca and ^{50}Ti have $N=28$, for which a neutron subshell is closed. Both Figures 8a and 8b have been evaluated shortly after photodisintegration has initiated core collapse, which will then be subsequently sustained by the reduction of the outward pressure through electron-capture and the resulting almost complete neutronization of the core.

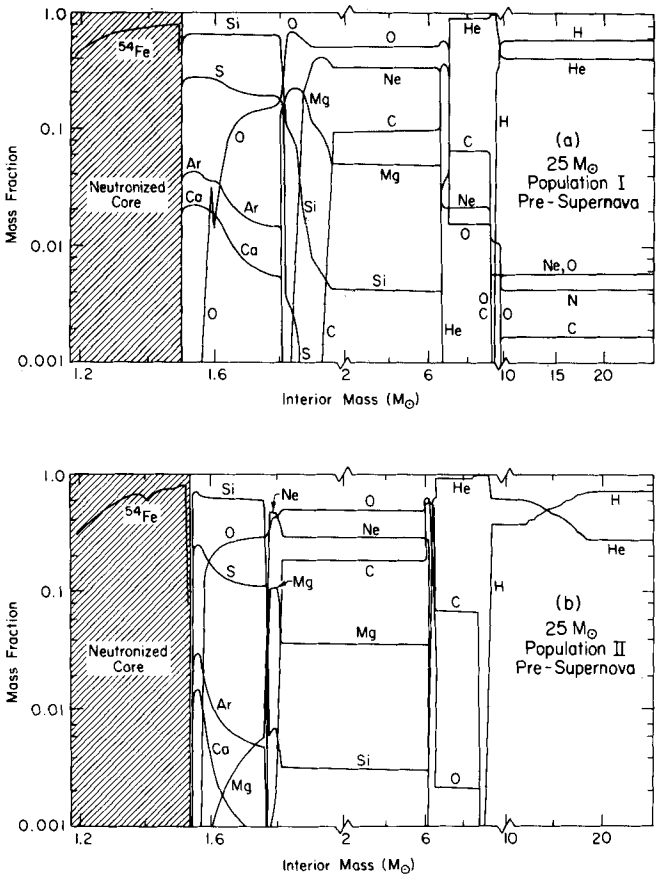

Fig. 8. Pre-supernova abundances by mass fraction versus increasing interior mass in solar masses $M_\odot$, measured from zero at the stellar center to $25\,M_\odot$, the total stellar mass from *Woosley* and *Weaver* [38]. a) (above) Population I star. b) (below) Population II star.

It must be realized that the various burning stages took place originally over the central regions of the star and finally in a shell surrounding that region. Subsequent stages modify the inner part of the previous burning stage. For example, in the 25 solar mass Population I star of Figure 8a, C-burning took place in the central 6.5 solar masses of the star, but the inner 1.9 solar masses were modified by subsequent Ne-, O-, and Si-burning.

Helium burning produces a stellar core consisting mainly of ^{12}C and ^{16}O. After core contraction, the temperature and density rise until carbon burning through $^{12}C+{}^{12}C$ fusion is ignited. The S-factor for the total reaction rate shown in Figure 10 has been taken from page 213 of [33] and is based on measurements in a number of laboratories. The extrapolation to the low energies of astrophysical relevance is uncertain, as Figure 10 makes clear, and more experimental and theoretical studies are urgently needed. At the lowest bombarding energy, 2.4 MeV, the cross section is ca. 10^{-8} barns. For a representative burning temperature of 6×10^8 K, the effective energy is $E_0=1.7$ MeV, and the extrapolated cross section is ca. 10^{-13} barns. The main product of carbon burning is ^{20}Ne produced primarily in the $^{12}C(^{12}C,\alpha)^{20}Ne$ reaction. The reactions $^{12}C(^{12}C,p)^{23}Na$ and $^{12}C(^{12}C,n)^{23}Mg(e^+\nu)^{23}Na$ also occur, as well as many secondary reactions such as $^{23}Na(p,\alpha)^{20}Ne$. When the ^{12}C is exhausted, ^{20}Ne and ^{16}O are the major remaining constituents. As the temperature rises, from further gravitational contraction, the ^{20}Ne is destroyed by photodisintegration, $^{20}Ne(\gamma,\alpha)^{16}O$. This occurs because the alpha-particle in ^{20}Ne is bound to its closed-shell partner, ^{16}O, by only 4.731 MeV. In ^{16}O, for example, the binding of an alpha-particle is 7.162 MeV.

The next stage is oxygen burning through $^{16}O+{}^{16}O$ fusion. The S-factor for the total reaction rate is shown in Figure 11 and is based entirely on data obtained in the Kellogg Laboratory at Caltech. The work of *Hulke, Rolfs,*

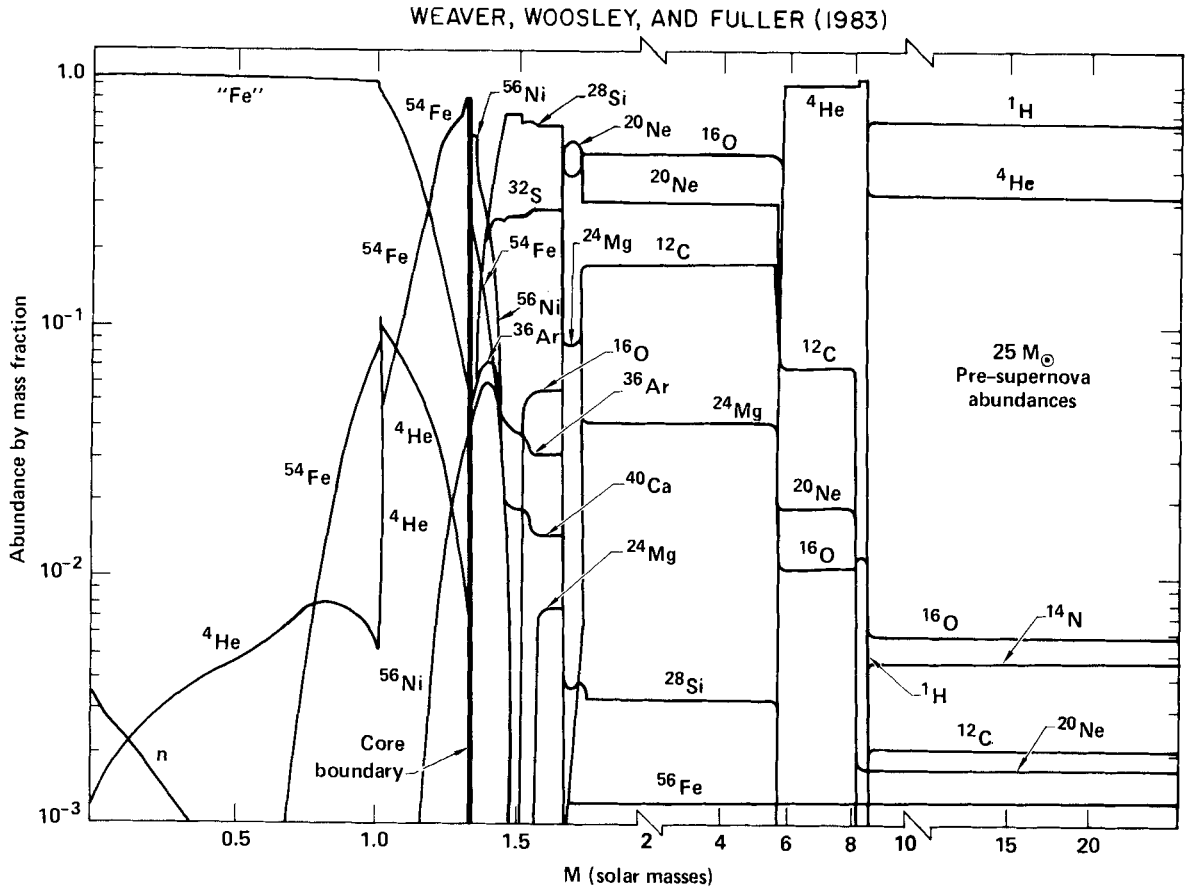

Fig. 9. Pre-supernova abundances by mass fraction versus increasing interior mass for a Population I star with total mass equal to 25 $M_\odot$ (from *Weaver, Woosley,* and *Fuller* [39]).

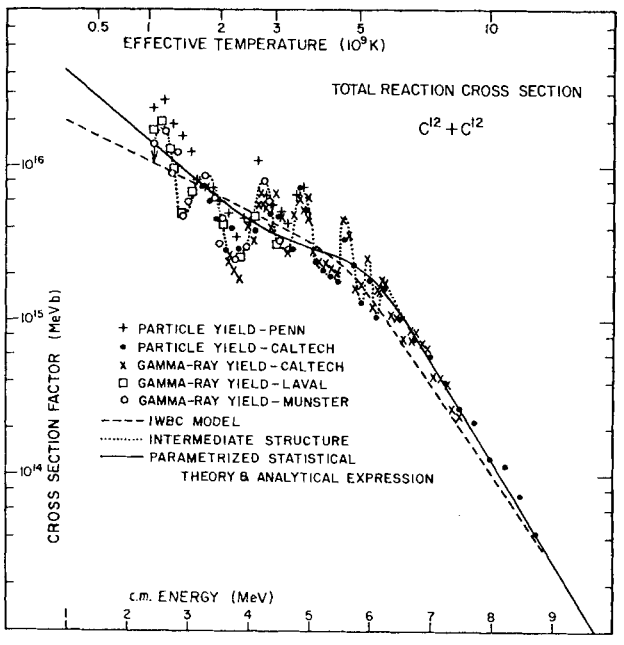

Fig. 10. The total cross-section factor in MeVb versus center-of-momentum energy in MeV for the fusion of ^{12}C and ^{12}C. The experimental data from several laboratories are shown along with schematic intermediate structure in the dotted curve. Two parametrized adjustments to the data, ignoring intermediate structure, are shown in the dashed and solid curves.

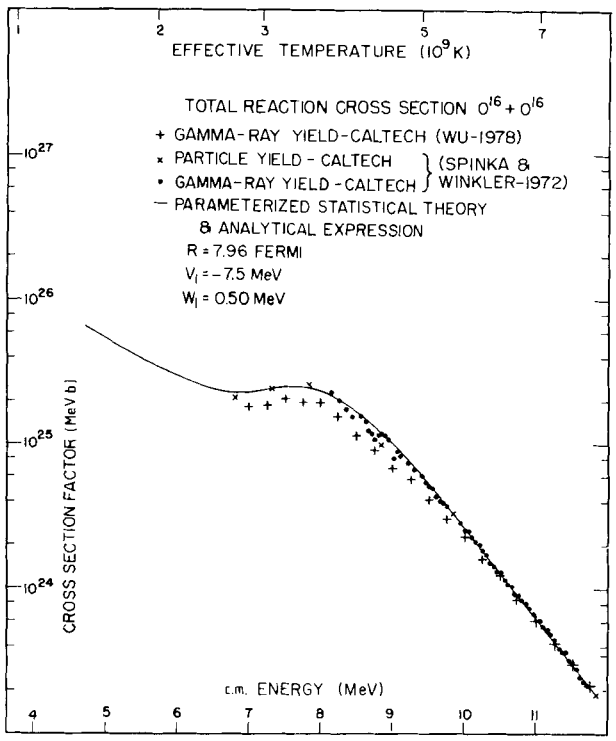

Fig. 11. The total cross-section factor in MeVb versus center-of-momentum energy in MeV for the fusion of ^{16}O + ^{16}O. The experimental data from several measurements at Caltech are shown and compared with a parametrized theoretical adjustment in the solid curve.

and *Trautvetter*[40] using gamma-ray detection is in fair agreement with the gamma-ray measurements at Caltech. As in the case of $^{12}C + ^{12}C$, the extrapolation to the low energies of astrophysical relevance is uncertain, although only one of many possible extrapolations is shown in Figure 11. The main product of oxygen burning is ^{28}Si through the primary reaction $^{16}O(^{16}O,\alpha)^{28}Si$ and a number of secondary reactions. Under some conditions, neutron-induced reactions lead to the synthesis of significant quantities of ^{30}Si. Oxygen burning can result in nuclei with a small but important excess of neutrons over protons.

The onset of Si-burning signals a marked change in the nature of the *fusion process*. The Coulomb barrier between two ^{28}Si nuclei is too great for fusion to produce the compound nucleus ^{56}Ni directly at the ambient temperatures ($T_9 = 3$ to 5) and densities ($\rho = 10^5$ to 10^9 g cm^{-3}). However, the ^{28}Si and subsequent products are easily photodisintegrated by (γ,α), (γ,n) and (γ,p)-reactions. As Si-burning proceeds, more and more ^{28}Si is reduced to nucleons and alpha particles, which can be captured by the remaining ^{28}Si nuclei to build through the network in Figure 7 up to the iron group nuclei. The main product in explosive Si-burning is ^{56}Ni, which transforms eventually through two beta-decays to ^{56}Fe.

In quasistatic Si-burning, the weak interactions are so fast enough that ^{54}Fe, with two more neutrons than protons, is the main product. Because of the important role played by alpha particles (α) and the inexorable trend to equilibrium (e) involving nuclei near mass 56, which have the largest binding energies per nucleon of all nuclear species, B^2FH[18] broke down what is now called Si-burning into an α-process and an e-process. Quasi-equilibrium calculations for Si-burning were made by *Bodansky, Clayton,* and *Fowler*[41], who cite the original papers in which the basic ideas of Si-burning were developed. Modern computers permit detailed network flow calculations to be made, as discussed in references [38] and [39].

The extensive laboratory studies of Si-burning reactions are reviewed in [33]. Figures 12 and 13, adapted from *Zyskind* et al.[42], show the laboratory excitation curves for $^{54}Cr(p,n)^{54}Mn$ and $^{54}Cr(p,\gamma)^{55}Mn$ as examples. The neutrons produced in the first of these reactions will increase the number of neutrons available in Si-burning, but will not contribute directly to the synthesis of ^{55}Mn as does the second reaction. In fact, above its threshold at 2.158 MeV the (p,n)-reaction competes strongly with the (p,γ)-reaction, which is of primary interest, and produces the pronounced *competition cusp* in the excitation curve in Figure 13. Competition in the disintegration of the compound nucleus produced in nuclear reactions was stressed very early by *Niels Bohr*, so perhaps the cusps should be called *Bohr cusps*. They arise from the same basic cause but are not the long known *Wigner cusps*. It will be clear from Figure 13 that the rate of the $^{54}Cr(p,\gamma)^{55}Mn$ reaction at very high temperature will be an order of magnitude lower, because of the cusp, than would otherwise be the case.

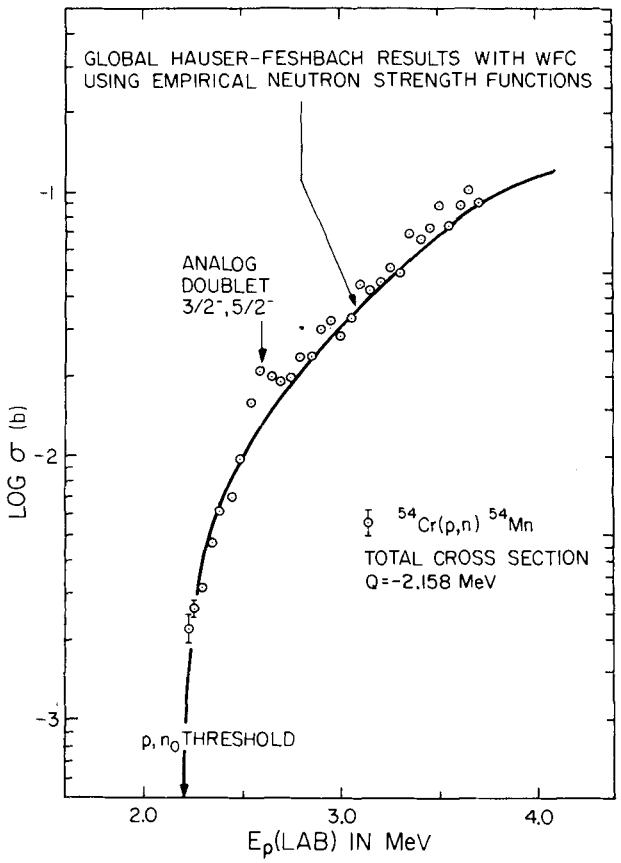

Fig. 12. The total cross section in barns integrated over all outgoing angles versus laboratory proton energy in MeV for the reaction $^{54}Cr(p,n)^{54}Mn$. The data of *Zyskind* et al. [42] are compared with unnormalized global Hauser-Feshbach calculations made by *Woosley* et al. [23].

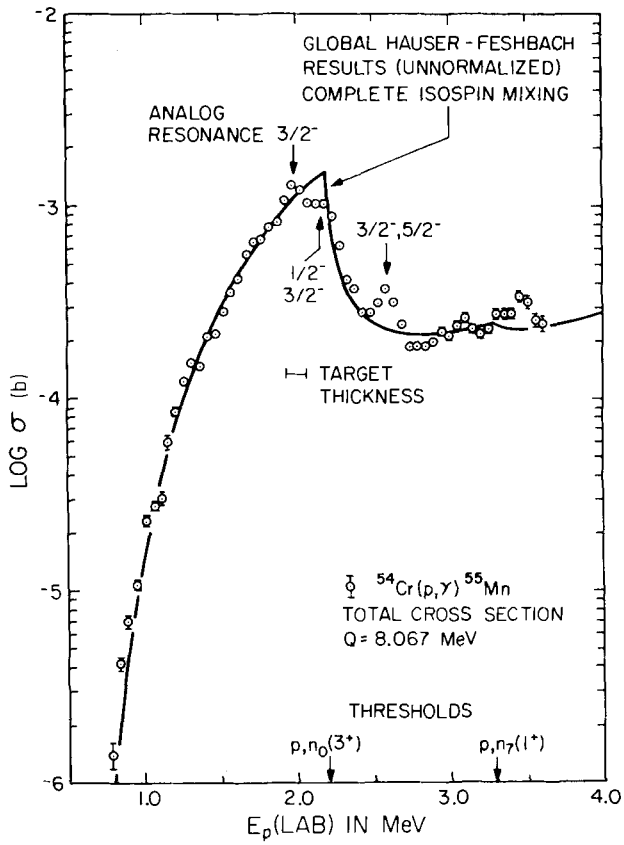

Fig. 13. The total cross section in barns integrated over all outgoing angles versus laboratory proton energy in MeV for the reaction $^{54}Cr(p,\gamma)^{55}Mn$. The data of *Zyskind* et al. [42] are compared with unnormalized global Hauser-Feshbach calculations made by *Woosley* et al. [23].

The element manganese has only one isotope, ^{55}Mn. The manganese in nature is produced in quasistatic Si-burning, most probably through the ^{54}Cr$(p,\gamma)^{55}$Mn-reaction discussed in the previous paragraph. The reaction network extends to ^{54}Cr and then on through ^{55}Mn. ^{51}V$(\alpha,\gamma)^{55}$Mn and ^{52}V$(\alpha,n)^{55}$Mn may also contribute, especially in explosive Si-burning. The overall synthesis of ^{55}Mn involves a balance in its production and destruction. In quasistatic Si-burning, the reactions which destroy ^{55}Mn are most probably ^{55}Mn$(p,\gamma)^{56}$Fe and ^{55}Mn$(p,n)^{55}$Fe, which are discussed and illustrated by *Mitchell* and *Sargood*[43]. ^{55}Mn$(\alpha,\gamma)^{59}$Co, ^{55}Mn$(\alpha,p)^{58}$Fe, and ^{55}Mn$(\alpha,n)^{58}$Co may also destroy some ^{55}Mn in explosive Si-burning. In the figures discussed in Section VIII, it will be noted that calculations of the overall synthesis of ^{55}Mn yield values in fairly close agreement with the abundance of this nucleus in the solar system. Unfortunately, the same can not be said about many other nuclei.

The laboratory measurements on Si-burning reactions have covered only about 20% of the reactions in the network of Figure 7 involving stable nuclei as targets. Direct measurements on short-lived radioactive nuclei and the excited states of all nuclei are impossible at the present time. In this connection, the production of radioactive ion-beams holds great promise for the future. *Richard Boyd* and *Haight* et al.[44] have pioneered the development of this technique.

Figures 14 and 15 show the beam transport system developed by *Haight* et al.[44], which has produced accelerated beams of ^{7}Be and ^{13}N and successfully determined the cross section of the reaction ^{2}H(^{7}Be,^{8}B)n to be 59 ± 11 mb for 16.9 MeV ^{7}Be-ions. The equivalent center-of-momentum energy for the ^{7}Be$(d,n)^{8}$B reaction is 3.8 MeV. It is my view that continued development and application of radioactive ion-beam techniques could bring the most exciting results in laboratory Nuclear Astrophysics in the next decade. For example, the rate of the ^{13}N$(p,\gamma)^{14}$O reaction, which will be studied as ^{1}H(^{13}N,γ)^{14}O, is crucial to the operation of the so-called fast CN-cycle.

In any case it has been clear for some time that experimental results on Si-burning reactions must be systematized and supplemented by comprehensive theory. Fortunately, theoretical average cross sections suffice in many cases. This is because the stellar reaction rates integrate the cross sections over the Maxwell-Boltzmann distribution. For most Si-burning reactions resonances in the cross section are closely spaced and even overlapping, and the integration covers a wide enough range of energies that the detailed structure in the cross sections is automatically averaged out. The statistical model of nuclear reactions developed by *Hauser* and *Feshbach*[45], which yields average cross sections, is ideal for the purpose. Accordingly, *Holmes, Woosley, Fowler,* and *Zimmerman*[46] undertook the task of developing a *global, parametrized* Hauser-Feshbach theory and computer program for use in Nuclear Astrophysics. An extension of this work is reported in [23]. The free parameters are the radius, depth, and compensating reflection factor of the black-body, square-well equivalent of the Woods-Saxon potential characteristic of the interaction between n, p, and α with nuclei having $Z \geq 8$. Two free-parameters must also be incorporated to adjust the intensity of electric and magnetic dipole transitions for gamma radiation. Weak interaction rates must also be specified, and ways of doing this will be discussed later in Section VII.

The parameters originally chosen for N, p, and α-reactions were taken from earlier work of *Michaud* and *Fowl-*

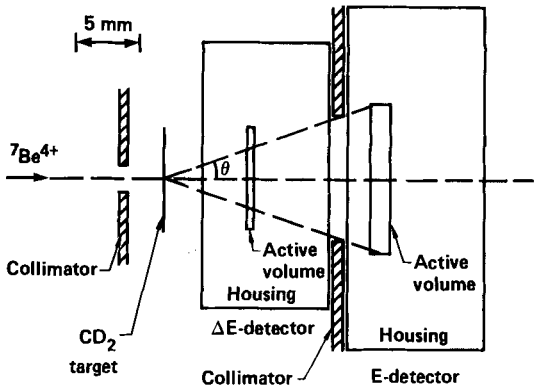

Fig. 15. Detail of the target and detector in the radioactive beam transport system developed by *Haight* et al. [44].

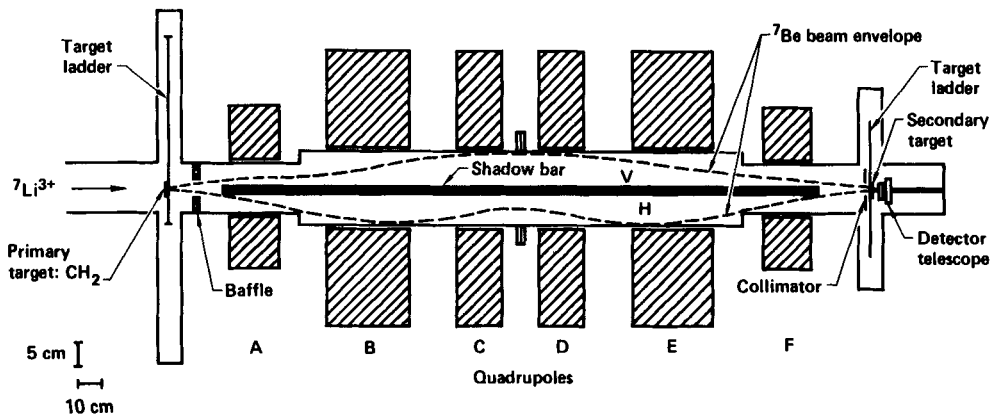

Fig. 14. Radioactive beam transport system developed by *Haight* et al. [44].

er[47], who depended heavily on studies by *Vogt* (see [47]). These parameters and those chosen for electromagnetic and weak interactions have survived comparison of the theory with a plethora of laboratory measurements. More sophisticated programs have been developed which use experimental neutron strength functions instead of that from the equivalent square well or which use realistic Woods-Saxon potentials for all interactions, as done by *Mann*[48]. In addition, marked improvement in the correspondence between theory and experiment is found when width-fluctuation corrections are made, as described in *Zyskind* et al.[49].

It is well known that the free parameters can always be adjusted to fit the cross sections and reaction rates of any one particular nuclear reaction. This is not done in a *global* program. The parameters are, in principle, determined by the best least-squares fit to all reactions for which experimental results are available. For example, see the figure on p. 307 of [46]. It is on this basis that some confidence can be had in predictions in those cases where experimental results are unavailable.

The original program[23,46] has produced reaction rates, either in numerical or analytical form, as a function of temperature. Ready comparison with integrations of laboratory cross sections for target ground states are possible. Using the same *global* parameters which apply to reactions involving the ground states of stable nuclei, the theoretical program calculates rates for the ground states of radioactive nuclei and for the excited states of both stable and radioactive nuclei. Summing over the statistically weighted contributions of the ground and known excited states or theoretical level density functions, we obtain the stellar reaction rate for the equilibrated statistical population of the nuclear states. After summing, division by the partition function of the target nucleus is necessary. Analytical parametrized expressions for the partition functions of nuclei with $8 \leq Z \leq 36$ are given in Table II A of [23] as a function of temperature over the range $0 \leq T \leq 10^{10}$ K.

Sargood[50] has compared experimental results from a number of laboratories for protons and alpha particles reacting with 80 target nuclei, which are, of course, in their ground states, with the theoretical predictions made in [23]. Ratios of statistical model calculations to laboratory measurements for 12 cases are shown in Table 3 for temperatures in the range 1 to 5×10^9 K. The double entry for $^{27}Al(p,n)^{27}Si$ signifies ratios of theory to measurements made in two different laboratories. It is fair to note that the theoretical calculations match the experimental results within 50% with a few marked exceptions. In American vernacular "You win some and you lose some". For the rather light targets in Table 3, especially at low temperature, the global mean rates can be in error whenever more and stronger resonances or fewer and weaker resonances than expected on average occur in the excitation curve of the reaction at low energies.

Sargood[50] has also compared the ratio of the stellar rate of a reaction with target nuclei in a thermal distribution of ground and excited states with the rate for all target nuclei in their ground state. The latter is of course determined from laboratory measurements. A number of cases are tabulated for $T = 5 \times 10^9$ K in Table 4. In many cases, notably

Table 3. Statistical model calculations versus measurements: Ratio of reaction rate (ground state of target) from *Woosley, Fowler, Holmes,* and *Zimmerman* [23] to reaction rates from experimental yield measurements (1970–1982) at Bombay, Caltech, Colorado, Kentucky, Melbourne, and Toronto.

Reaction	$T_9 = T/10^9$ [K]				
	1	2	3	4	5
$^{23}Na(p,n)^{23}Mg$	1.4	1.2	1.1	1.1	1.0
$^{25}Mg(p,\gamma)^{26}Al$	1.2	1.1	1.0	0.9	0.8
$^{25}Mg(p,n)^{25}Al$	1.1	1.0	0.9	0.8	0.8
$^{27}Al(p,\gamma)^{28}Si$	3.7	2.1	1.5	1.3	1.1
$^{27}Al(p,n)^{27}Si$	1.8	1.4	1.3	1.3	1.2
	0.9	0.9	0.9	1.0	1.0
$^{28}Si(p,\gamma)^{29}P$		1.2	1.3	1.2	0.9
$^{29}Si(p,\gamma)^{30}P$		1.0	1.6	1.6	1.5
$^{39}K(p,\gamma)^{40}Ca$	15	4.5	3.0	2.6	2.5
$^{41}K(p,\gamma)^{42}Ca$	0.5	0.5	0.5	0.4	0.4
$^{41}K(p,n)^{41}Ca$	0.8	1.0	1.1	1.2	1.3
$^{40}Ca(p,\gamma)^{41}Sc$				0.1	0.2
$^{42}Ca(p,\gamma)^{43}Sc$	1.3	1.4	1.4	1.4	1.3
	0.8	1.1	1.3	1.4	1.4

Table 4. Stellar/laboratory reaction rates: $\langle \sigma v \rangle^* / \langle \sigma v \rangle^\circ$; $T = 5 \times 10^9$ K; after *D. G. Sargood* [50] as well as *Woosley, Fowler, Holmes,* and *Zimmerman* [23].

Target-nucleus	Reaction								
	(n,γ)	(n,p)	(n,α)	(p,γ)	(p,n)	(p,α)	(α,γ)	(α,n)	(α,p)
^{20}Ne	0.959	12.2	4.98	0.954	34.1	6.86	0.907	4.90	1.29
^{21}Ne	0.808	6.15	1.13	0.818	1.78	19.5	0.943	0.985	1.37
^{22}Ne	0.917	159	22.1	0.895	5.11	2.72	0.968	0.996	2.46
^{23}Na	0.897	4.95	9.70	0.890	2.27	0.944	0.826	1.30	0.918
^{24}Mg	0.939	20.4	7.30	0.924	120	15.0	0.835	4.70	1.04
^{25}Mg	0.905	5.05	3.18	0.862	3.48	5.02	0.958	0.973	1.10
^{26}Mg	0.968	71.4	53.8	0.958	8.05	4.92	0.974	1.00	1.41
^{27}Al	0.934	4.12	10.9	0.913	3.22	1.14	0.905	1.13	0.972
^{28}Si	0.976	6.51	7.26	0.950	140	23.5	0.933	3.55	1.02
^{29}Si	0.943	8.67	3.34	0.907	3.18	50.1	0.927	0.964	1.18
^{30}Si	0.989	89.4	28.6	0.982	2.99	6.63	0.973	1.01	1.09
^{31}P	0.972	2.63	18.4	0.901	3.77	1.11	0.969	1.70	0.978
^{32}S	0.988	2.33	1.57	0.980	90.1	7.35	0.975	3.79	1.00
^{33}S	0.943	1.46	1.06	0.920	4.73	3.24	0.916	0.995	1.01
^{34}S	1.00	25.8	13.1	0.979	8.02	2.02	0.964	1.05	1.02
^{36}S	0.998	428	95.9	1.00	1.00	1.02	0.995	1.00	1.68
^{35}Cl	0.972	1.19	3.06	0.948	4.48	1.05	0.945	1.23	0.992
^{37}Cl	0.994	26.0	13.7	0.987	1.00	1.00	0.985	1.00	0.995

for reactions producing gamma rays, the ratio of stellar to laboratory rates is close to unity. In other cases the ratios can be high by several orders of magnitude. This can occur for a number of reasons. It frequently occurs when the ground state can interact only through partial waves of high angular momentum resulting in small penetration factors and thus small cross sections and rates. This makes clear a basic assumption in the prediction of stellar rates: a statistical theory which works well predicting ground state results is assumed to do equally well in predicting excited state results. This assumption is frequently not valid. *Bahcall* and *Fowler*[51] have shown that in a few cases laboratory measurements on inelastic scattering involving excited states can be used indirectly to determine reaction cross sections for those states.

Ward and *Fowler*[52] have investigated in detail the circumstances under which long-lived isomeric states do not come into equilibrium with ground states. When this occurs it is necessary to incorporate into network calculations the stellar rates for both the isomeric and ground state. An example of great interest is the nucleus ^{26}Al. The ground state has spin and parity, $J^{\pi}=5^{+}$, and isospin $T=0$, and has a mean lifetime for positron emission to ^{26}Mg of 10^6 years. The isomeric state at 0.228 MeV has $J^{\pi}=0^{+}$, $T=1$ and mean lifetime of 9.2 seconds. *Ward* and *Fowler*[52] show that the isomeric state effectively does not come into equilibrium with the ground state for $T<4\times10^8$ K. At these low temperatures, both the isomeric state and the ground state of ^{26}Al must be included in the network of Figure 7.

VII. Astrophysical Weak-Interaction Rates

Weak nuclear interactions play an important role in astrophysical processes in conjunction with the strong nuclear interactions, as indicated in Figure 7. Only through the weak interaction can the overall proton number and neutron number of nuclear matter change during stellar evolution, collapse, and explosion. The formation of a neutron star requires that protons in ordinary stellar matter capture electrons. Gravitational collapse of a Type II supernova core is retarded as long as electrons remain to exert outward pressure.

Many years of theoretical and experimental work on weak-interaction rates in the Kellogg Laboratory and elsewhere have culminated in the calculation and tabulation by *Fuller, Fowler,* and *Newman*[53] of electron and positron emission rates and continuum electron and positron capture rates, as well as the associated neutrino energy loss rates for free nucleons and 226 nuclei with mass numbers between $A=21$ and 60. Extension to higher and lower values for A is now underway.

These calculations depended heavily on experimental determinations in Kellogg by *Wilson, Kavanagh,* and *Mann*[54] of Gamow-Teller elements for 87 discrete transitions in intermediate-mass nuclei. The majority of the experimental matrix elements for both Fermi and Gamow-Teller discrete transitions as well as nuclear level data were taken from the exhaustive tabulation of *Lederer* and *Shirley*[55]. Unmeasured matrix elements for allowed transitions were assigned a mean value as described in the second reference in [53]. These mean values were $|M_F|^2=.062$ and $|M_{GT}|^2=.039$, corresponding to $\log ft=5$, where f is the phase-space factor and t is the half-life for the transition. Nuclear physicists traditionally think in terms of $\log ft$-values in connection with weak interaction rates.

Simple shell model arguments were employed to estimate Gamow-Teller sum rules and collective state resonance excitation energies. These estimates have been shown to be fair approximations for $T^{<}$-nuclei and $T^{>}$-nuclei by recent high resolution measurements on *p,n*-reactions and ^3T,^{3}He-reactions by *Goodman* et al. and *Ajzenberg-Selove* et al., respectively[56]. Here $T^{<}$, with $T\equiv|N-Z|$ represents, for example, ^{56}Fe with $T=2$ in ^{56}Fe$(e^-,\nu)^{56}$Mn or ^{56}Fe$(n,p)^{56}$Mn. Similarly, $T^{>}$ designates ^{56}Mn with $T=3$. The work described in [53] emphasizes the great need for additional results for $T^{>}$-nuclei using the *n,p*-reaction as well as the ^3T,^{3}He-reaction from which matrix elements for electron capture can be obtained.

Moment method shell model calculations of Gamow-Teller strength functions have been performed by *S. D. Bloom* and *G. M. Fuller*[57] with the Lawrence Livermore National Laboratory's vector shell model code for the ground states and first excited states of ^{56}Fe, ^{60}Fe, and ^{64}Fe. These detailed calculations confirm the general trends in Gamow-Teller strength distributions used in the approximations in [53].

The discrete state contribution to the rates, dominated by experimental information on the Fermi transitions, determines the weak nuclear rates in the regime of temperature and densities characteristic of the quasistatic phases of presupernova stellar evolution. At the higher temperatures and densities characteristic of the supernova collapse phase, which is of such great current interest, as discussed in detail in *Brown, Bethe,* and *Baym*[58], the electron-capture rates are dominated by the Gamow-Teller collective resonance contribution.

The detailed nature and the difficulty of the theoretical aspects of the combined atomic, nuclear, plasma, and hydrodynamic physics problems in Type II supernova implosion and explosion were brought home to us by *Hans Bethe* during his stay in our laboratory as a Caltech Fairchild Scholar early in 1982. His visit plus long-distance interaction with his collaborators resulted in the preparation of two seminal papers, *Bethe, Yahil,* and *Brown*[59] and *Bethe, Brown, Cooperstein,* and *Wilson*[60].

Current ideas on the nuclear equation of state predict that early in the collapse of the iron core of a massive star the nuclei present will become so neutron-rich that allowed electron capture on protons in the nuclei is blocked. Allowed electron capture, for which $\Delta l=0$, is not permitted when neutrons have filled the subshells having orbital angular momentum, l, equal to that of the subshells occupied by the protons.

This neutron shell blocking phenomenon, and several unblocking mechanisms operative at high temperature and density, including forbidden electron capture, have been studied in terms of the simple shell model by *Fuller*[61]. Though the unblocking mechanisms are sensitive to details of the equation of state, typical conditions result in a con-

siderable reduction of the electron capture rates on heavy nuclei, leading to significant dependence on electron capture by the small number of free protons and a decrease in the overall neutronization rate.

The results of one-zone collapse calculations carried out by *Fuller*[61] suggest that the effect of neutron shell blocking is to produce a larger core lepton fraction (leptons per baryon) at neutrino trapping. In keeping with the Chandrasekhar relation that core mass is proportional to the square of the lepton fraction, this leads to a larger *final*-core mass and hence a stronger post-bounce shock. On the other hand, the incorporation of the new electron capture rates during precollapse Si-burning reduces the lepton fraction and leads to a smaller *initial*-core mass and thus to a smaller amount of material (*initial*-core mass minus *final*-core mass) in which the post-bounce shock can be dissipated. The dissipation of the shock is thus reduced. This is discussed in detail in [39].

Recent work on the weak interaction has concentrated on making the previously calculated reaction rates as efficient as possible for users of the published tables and the computer tapes, which are made available on request. The stellar weak interaction rates of nuclei are in general very sensitive functions of temperature and density. Their temperature dependence arises from thermal excitation of parent excited states and from the lepton distribution functions in the integrands of the decay and continuum capture phase space factors.

For electron and positron emission, most of the temperature dependence is due to thermal population of parent excited states at all but the lowest temperatures and highest densities. In general, only a few transitions will contribute to these decay rates and hence the variation of the rates with temperature is usually not so large that rates cannot be accurately interpolated in temperature and density with the standard grids provided in [53]. The density dependence of these decay rates is minimal. In the case of electron emission, however, there may be considerable density dependence due to Pauli blocking for electrons where the density is high and the temperature is low. This does not present much of a problem for practical interpolation since the electron-emission rate is usually very small under these conditions.

The temperature and density dependence of continuum electron and positron capture is a much more serious problem. In addition to temperature sensitivity introduced through thermal population of parent excited states, there are considerable effects from the lepton distribution functions in the integrands of the continuum-capture phase-space factors. This sensitivity of the capture rates means that interpolation in temperature and density on the standard grid to obtain a rate can be difficult, requiring a high-order interpolation routine and a relatively large amount of computer time for an accurate value. This is especially true for electron capture processes with a threshold above zero energy.

We have found that the interpolation problem can be greatly eased by defining a simple continuum-capture, phase-space integral, based on the parent ground-state to daughter-ground state transition Q-value, and then dividing this by the tabulated rates[53] at each temperature and density grid point to obtain a table of effective *ft*-values; these turn out to be much less dependent on temperature and density. This procedure requires a formulation of the capture phase-space factors which is simple enough to use many times in the inner loop of stellar evolution nucleosynthesis computer programs. Such a formulation in terms of standard Fermi integrals has been found, along with approximations for the requisite Fermi integrals. When the chemical potential (Fermi energy) which appears in the Fermi integrals goes through zero, these approximations have continuous values and continuous derivatives.

We have recently found expressions for the reverse reactions to e^-, e^+-capture, (i.e., $\nu,\bar{\nu}$-capture) and for $\nu,\bar{\nu}$-blocking of the direct reactions when $\nu,\bar{\nu}$-states are partially or completely filled. These reverse reactions and the blocking are important during supernova core collapse when neutrinos and antineutrinos eventually become trapped, leading to equilibrium between the two directions of capture. General analytic expressions have been derived and approximated with computer-usable equations. All of these new results described in the previous paragraphs will be published by *Fuller, Fowler* and *Newman*[62], and new tapes including $\nu,\bar{\nu}$-capture will be made available to users on request.

VIII. Calculated Abundances for $A \lesssim 60$, with Brief Comments on Explosive Nucleosynthesis

Armed with the available strong and weak nuclear reaction rates which apply to the advanced stages of stellar evolution, theoretical astrophysicists have attempted to derive the elemental and isotopic abundances produced in quasistatic presupernova nucleosynthesis and in explosive nucleosynthesis occurring during supernova outbursts.

The various stages of preexplosive nucleosynthesis have been discussed in Sections IV, V, and VI, and it is fair to say that there is reasonably general agreement on nucleosynthesis during these stages. On the other hand, explosive nucleosynthesis is still an unsettled matter, subject to intensive study at the present time, as reviewed, for example, by *Woosley, Axelrod,* and *Weaver*[63].

The abundances produced in explosive nucleosynthesis must of necessity depend on the detailed nature of supernova explosions. Ideas concerning the nature of Type I and Type II supernova explosions were published many years ago by *Hoyle* and *Fowler*[64] and *Fowler* and *Hoyle*[65]. It was suggested that Type I supernovae of small mass were precipitated by the onset of explosive carbon burning under conditions of electron degeneracy where pressure is approximately independent of temperature. Carbon burning raises the temperature to the point where the electrons are no longer degenerate, and explosive disruption of the star results. For Type II supernovae of larger mass it was suggested that Si-burning produced iron-group nuclei, which have the maximum binding energies of all nuclei so that nuclear energy is no longer available. Subsequent photodisintegration and electron capture in the stellar core lead to core implosion and ignition of explosive nucleosynthesis in the infalling inner mantle which still contains nuclear fuel. These ideas have "survived" but, to say the

least, with considerable modification over the years, as indicated in the excellent review by *Wheeler*[66]. Modern views on Type II supernovae are given in [39-60] and on Type I supernovae by *Nomoto*[67].

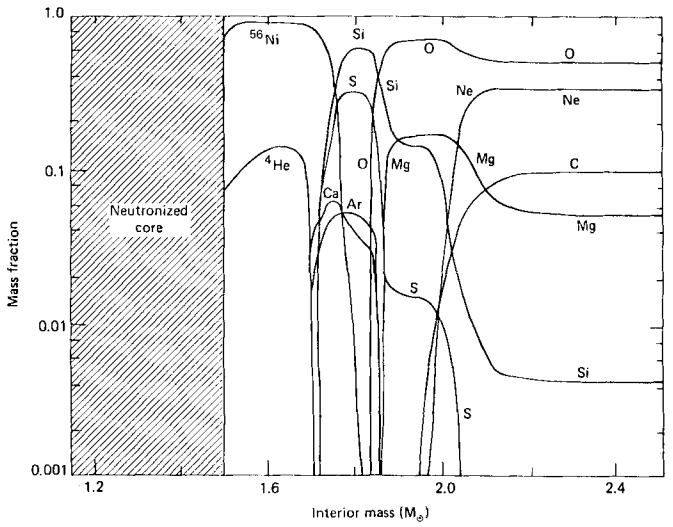

Fig. 16. Final abundances by mass fraction versus increasing interior mass in solar masses, $M_\odot$, in Type II supernova ejecta from a Population I star with total mass equal to $25M_\odot$, from *Woosley* and *Weaver*[38].

We can return to the nuclear abundance problem by reference to Figure 16, taken from [38], which shows the distribution of the final abundances by mass fraction in the supernova ejecta of a $25M_\odot$ Population I star. The presupernova distribution is that shown in Figure 8a. The modification in the abundances for the mass zones interior to $2.2M_\odot$ is very apparent. The mass exterior to $2.2M_\odot$ is ejected with little or no modification in nuclear abundances. The supernova explosion was simulated by arbitrarily assuming that approximately 10^{51} ergs was delivered to the ejected material by the shock generated in the bounce or rebound of the collapsing and hardening core.

Integration over the mass zones in Figure 16 for $1.5M_\odot < M < 2.2M_\odot$ and over those in Figure 8a for $M > 2.2M_\odot$ enabled *Woosley* and *Weaver*[38] to calculate the isotopic abundances ejected into the interstellar medium by their $25M_\odot$ Population I simulated supernova. The results relative to solar abundances (the reader should refer to the last paragraph of Section I) are show in Figure 17, which is taken from [38]. The relative ratios are normalized to unity for ^{16}O, for which the overproduction ratio was 14, i.e., for each gram of ^{16}O originally in the star, 14 grams were ejected. This overproduction in a single supernova can be expected to have produced the heavy-element abundances in the interstellar medium just prior to formation of the solar system, given that supernovae occur approximately every one hundred years in the Galaxy. The ultimate theoretical calculations will yield a constant overproduction factor of the order of 10.

The results shown in Figure 17 are disappointing if one expects the ejecta of $25M_\odot$ Population I supernovae to match solar system abundances with a relatively constant overproduction factor. The dip in abundances from sulfur to chromium is readily apparent. *Woosley* and *Weaver*[38] point out that calculations must be made for other stellar masses and properly integrated over the mass distribution for stellar formation, which varies roughly inversely proportional to mass. *Woosley, Axelrod,* and *Weaver*[63] discuss their expectations of the abundances produced in stellar explosions for stars in the mass range $10M_\odot$ to $10^6M_\odot$. They show that a $200M_\odot$ Population III star produces

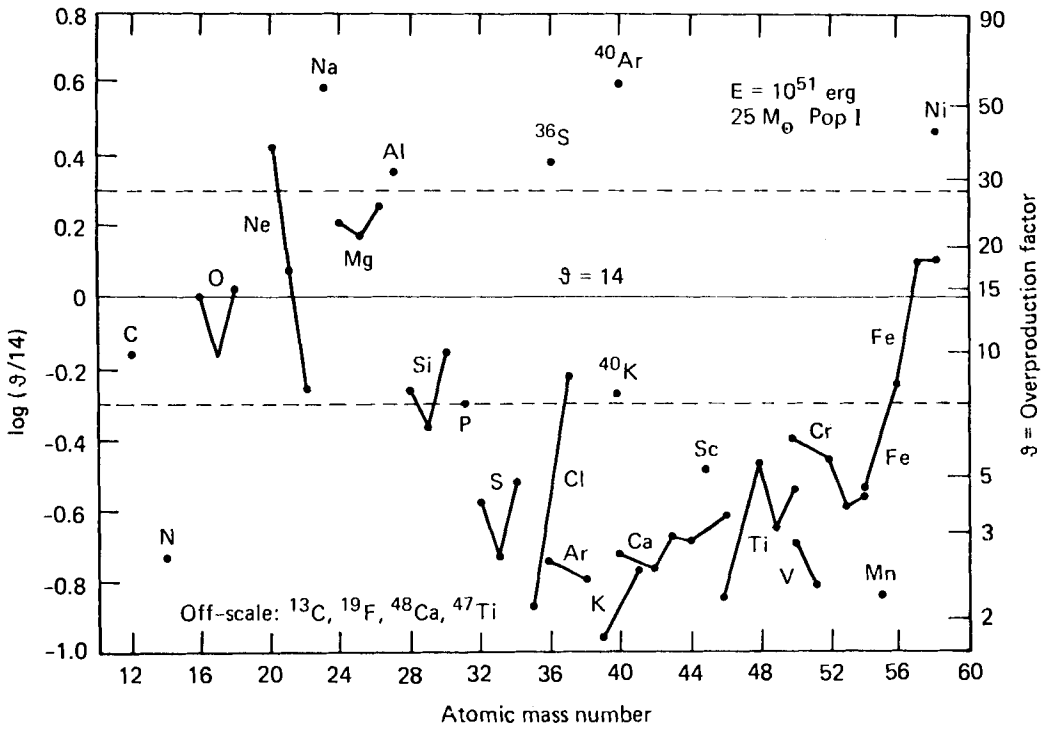

Fig. 17. Overabundance (ϑ) relative to 14 times solar abundances versus atomic mass number for nucleosynthesis resulting from a Type II, Population I supernova with total mass equal to $25M_\odot$, from *Woosley* and *Weaver* [38].

abundant quantities of sulfur, argon, and calcium which possibly compensate for the dip in Figure 17. Population III stars are massive stars in the range $100\,M_\odot < M < 300\,M_\odot$, which are thought to have formed from hydrogen and helium early in the history of the Galaxy and evolved very rapidly. Since their heavy element abundance was zero, they have no counterparts in presently forming Population I stars as well as no counterparts among old, low-mass Population II stars.

Other authors have suggested a number of solutions to the problem depicted in Figure 17. *Nomoto, Thielemann,* and *Wheeler*[68] have calculated the abundances produced in carbon deflagration models of Type I supernovae. By adding equal contributions from Type I and Type II supernovae, they obtain Figure 18, which can be considered somewhat more satisfactory than Figure 17. On the other hand, *Arnett* and *Thielemann*[69] have recalculated quasistatic presupernova nucleosynthesis for $M \approx 20\,M_\odot$, using a value for the $^{12}C(\alpha,\gamma)^{16}O$ rate equal to three times that given in [21]. This would seem to be justified by the recent analysis of $^{12}C(\alpha,\gamma)^{16}O$ data in [34], as discussed in Section V. These authors then assume that explosive nucleosynthesis will not substantially modify their quasistatic abundances and obtain the results shown in Figure 19. The average overproduction ratio is roughly 14, and deviations are in general within a factor of two of this value. However, their assumption of minor modification during explosion and ejection is questionable.

I feel that the results discussed in this section and those obtained by numerous other authors show promise of an eventual satisfactory answer to the question where and how did the elements from carbon to nickel originate. We shall see!

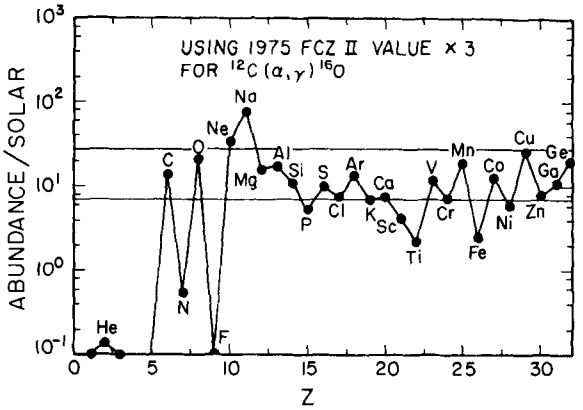

Fig. 19. Over-abundance yields relative to solar versus atomic number, Z, resulting from the explosion of a Type II supernova with mass approximately equal to $20\,M_\odot$, from *Arnett* and *Thielemann* [69]. The horizontal lines are a factor two higher and lower than the average overabundance equal to 14. It is assumed that the presupernova abundances were not modified during the supernova explosion. The reaction rate for $^{12}C(\alpha,\gamma)^{16}O$ of *Fowler, Caughlan,* and *Zimmerman* [21] was multiplied by a factor of 3, in accordance with the theoretical analysis by *Laganke* and *Koonin* [34].

IX. Isotopic Anomalies in Meteorites and Observational Evidence for Ongoing Nucleosynthesis

Almost a decade ago, it became clear that nucleosynthesis occurred in the Galaxy up to the time of formation of the solar system or at least up to several million years before its formation. For slightly over one year, it has been clear that nucleosynthesis continues up to the present time or at least within several million years of the present. The decay of radioactive $^{26}Al(\bar{\tau} = 1.04 \times 10^6$ years) is the key to these statements, which bring great satisfaction to most ex-

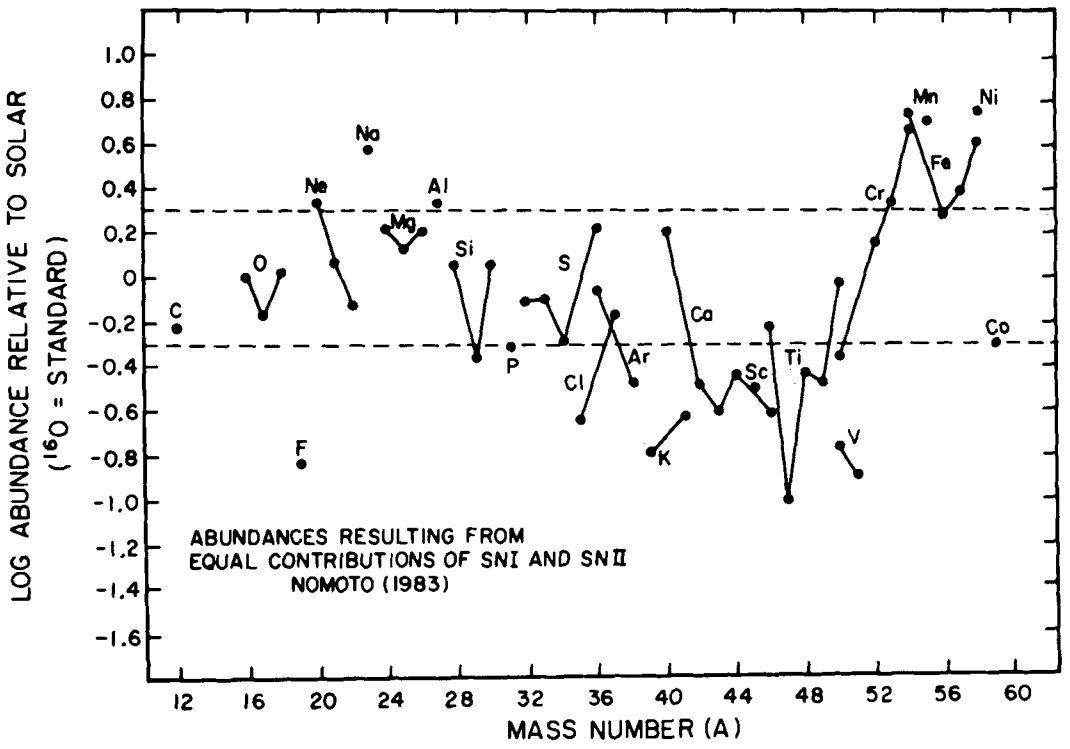

Fig. 18. Abundances relative to solar with the abundance of ^{16}O taken as standard produced by equal contributions from typical Type I and Type II supernovae, from *Nomoto, Thielemann,* and *Wheeler* [68].

perimentalists, theorists, and observers in Nuclear Astrophysics. For the record, it must be admitted that the word "clear" is subject to certain reservations in the minds of some investigators, but as a believer, "clear" is clear to me.

Isotopic anomalies in meteorites produced by the decay of short-lived radioactive nuclei were first demonstrated in 1960 by *Reynolds*[70], who found large enrichments of ^{129}Xe in the Richardson meteorite. *Jeffery* and *Reynolds*[71] demonstrated in 1961 that the excess ^{129}Xe correlated with ^{127}I in the meteorite and thus showed that the ^{129}Xe resulted from the decay in situ of ^{129}I ($\bar{\tau} = 23 \times 10^6$ years). Quantitative results indicated that $^{129}I/^{127}I \approx 10^{-4}$ at the time of meteorite formation. On the assumption that ^{129}I and ^{127}I are produced in roughly equal abundances in nucleosynthesis (most probably in the *r*-process) over a period of ca. 10^{10} years in the Galaxy prior to formation of the solar system, and taking into account that only the ^{129}I produced over a period of the order of its lifetime survives, *Wasserburg, Fowler,* and *Hoyle*[72] suggested that a period of free decay of the order of 10^8 years or more occurred between the last nucleosynthetic event which produced ^{129}I and its incorporation into meteorites in the solar system. There remains evidence for such a period in some cases, notably ^{244}Pu, but probably not in the history of the nucleosynthetic events which produced ^{129}I and other "short"-lived radioactive nuclei such as ^{26}Al and ^{107}Pd ($\bar{\tau} = 9.4 \times 10^6$ years).

The substantiated meteoritic anomalies in ^{26}Mg from ^{26}Al, in ^{107}Ag from ^{107}Pd, in ^{129}Xe from ^{129}I, and in the heavy isotopes of Xe from the fission of ^{244}Pu ($\bar{\tau} = 117 \times 10^6$ years; fission tracks also observed), as well as searches in the future for anomalies in ^{41}K from ^{41}Ca ($\bar{\tau} = 0.14 \times 10^6$ years), in ^{60}Ni from ^{60}Fe ($\bar{\tau} = 0.43 \times 10^6$ years), in ^{53}Cr from ^{53}Mn ($\bar{\tau} = 5.3 \times 10^6$ years), and in ^{142}Nd from ^{146}Sm ($\bar{\tau} = 149 \times 10^6$ years; α-decay) are discussed exhaustively by my colleagues *Wasserburg* and *Papanastassiou*[73]. They espouse in situ decay for the observations to date, but my former student *D. D. Clayton*[74] argues that the anomalies occur in interstellar grains preserved in the meteorites and originally produced by condensation in the expanding and cooling envelopes of supernovae and novae. *Wasserburg* and *Papanastassiou*[73] write on p. 90: "There is, as yet, no compelling evidence for the presence of preserved presolar grains in the solar system. All of the samples so far investigated appear to have melted or condensed from a gas, and to have chemically reacted to form new phases". With mixed emotions I accept this.

Before turning to some elaboration of the $^{26}Al/^{26}Mg$ case, it is appropriate to return to a discussion of the free-decay interval mentioned above. It is the lack of a detectable anomaly in ^{235}U from the decay of ^{247}Cm ($\bar{\tau} = 23 \times 10^6$ years) in meteorites, as shown by *Chen* and *Wasserburg*[75], coupled with the demonstrated occurrence of heavy Xe anomalies from the fission of ^{244}Pu ($\bar{\tau} = 117 \times 10^6$ years), as discussed, for example, by *Burnett, Stapanian,* and *Jones*[76], which demands a free-decay interval of the order of several times 10^8 years. This interval is measured from the "last" *r*-process nucleosynthesis event (supernova?) which produced the actinides, Th, U, Pu, Cm and beyond, up to the "last" nucleosynthesis events (novae?, supernovae with short-run *r*-processes?) which produced the short-lived nuclei ^{26}Al, ^{107}Pd, and ^{129}I before the formation of the solar system. The fact that the anomalies produced by these short-lived nuclei relative to normal abundances are all of the order of 10^{-4}, despite a wide range in their mean lifetimes (1.04 to 23×10^6 years), indicates that this anomaly range must be the result of inhomogeneous mixing of exotic materials with much larger quantities of normal solar-system materials over a short time, rather than the result of free decay. The challenges presented by this conclusion are manifold. Figure 14 from [73] shows the time scale for the formation of dust, rain, and hailstones in the early solar system and for the aggregation into chunks and eventually the terrestrial planets. The solar nebula was almost but not completely mixed when it collapsed to form the solar system. From ^{26}Al, it becomes clear that the mixing time down to an inhomogenity of only one part in 10^3 (see below) was the order of 10^6 years.

Evidence that ^{26}Al was alive in interstellar material in the solar nebula which condensed and aggregated to form the parent body (planet in the asteroid belt?) of the Allende meteorite is shown in Figure 20, taken with some modification from *Lee, Papanastassiou,* and *Wasserburg*[77]. The Allende meteorite fell near Pueblito de Allende in Mexico on February 8, 1969 and is a carbonaceous chondrite, a type of meteorite thought to contain the most primitive material in the solar system *unaltered since its original solidification.*

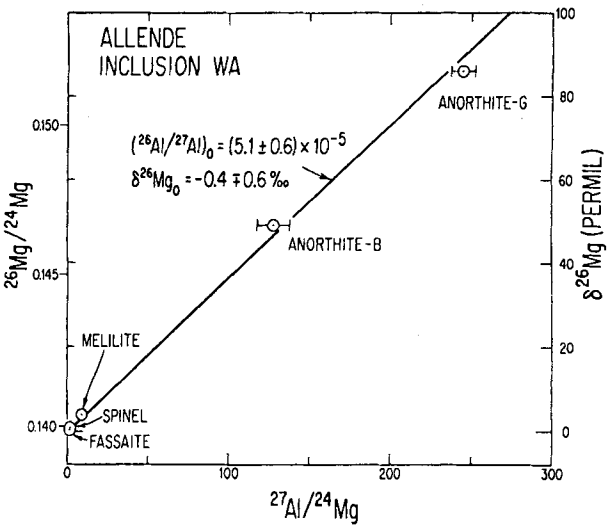

Fig. 20. Evidence for the in situ decay of ^{26}Al in various minerals in inclusion WA of the Allende meteorite from *Lee, Papanastassiou,* and *Wasserburg* [77]. The linear relation between $^{26}Mg/^{24}Mg$ and $^{27}Al/^{24}Mg$ implies that $^{26}Al/^{27}Al = (5.1 \pm 0.6) \times 10^{-5}$ at the time of formation of the inclusion with ^{26}Al considered to react chemically in the same manner as ^{27}Al.

Figure 20 depicts the results for $^{26}Mg/^{24}Mg$ versus $^{27}Al/^{24}Mg$ in different mineral phases (spinel, etc.) from a Ca-Al-rich inclusion called WA obtained from a chondrule found in Allende. It will be clear that excess ^{26}Mg correlates linearly with the amount of ^{27}Al in the mineral phases. Since ^{26}Al is chemically identical with ^{27}Al, it can be inferred that phases rich in ^{27}Al were initially rich in ^{26}Al, which subsequently decayed in situ to produce excess ^{26}Mg. ^{26}Al was alive with abundance 5×10^{-5} that of ^{27}Al

in one part of the solar nebula when the WA inclusion aggregated during the earliest stages of the formation of the solar system. The unaltered inclusion survived for 4.5 billion years to tell its story. Other inclusions in Allende and other meteorites yield $^{26}Al/^{27}Al$ ratios from zero up to $\approx 10^{-3}$, with 10^{-4} a representative value. The reader is referred to [73] for the rich details of the story and the importance and significance of non-accelerator-based contributions to Nuclear Astrophysics.

Evidence that ^{26}Al is alive in the interstellar medium today is shown in Figure 21, taken from *Mahoney, Ling, Wheaton,* and *Jacobson*[78], my colleagues at Caltech's Jet Propulsion Laboratory (JPL). Figure 21 shows the gamma-ray spectrum observed in the range 1760 to 1824 keV by instruments aboard the High Energy Astronomical Observatory, HEAO 3, which searched for diffuse gamma-ray emission from the Galactic equatorial plane.

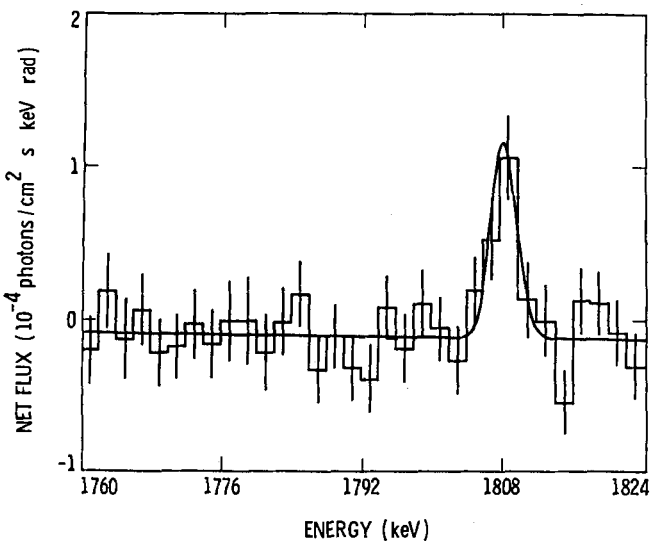

Fig. 21. The High Energy Astrophysical Observatory (HEAO 3) data on gamma rays in the energy range 1760 to 1824 keV emitted from the Galactic equatorial plane, from *Mahoney* et al. [78]. The line at 1809 keV is attributed to the decay of radioactive $^{26}Al(\bar{\tau} = 1.04 \times 10^6$ years) to the excited state of ^{26}Mg at this energy.

The discrete line at 1809 keV, detected with a significance of nearly five standard deviations, is without doubt due to the transition from the first excited state at 1809 keV in ^{26}Mg to its ground state. Radioactive ^{26}Al decays by $^{26}Al(e^+\nu)^{26}Mg^*(\gamma)^{26}Mg$ to this state and thence to the ground state of ^{26}Mg. This gamma-ray transition shows clearly that ^{26}Al is alive in the interstellar medium in the Galactic equatorial plane today. Given the mean lifetime (1.04×10^6 years) of ^{26}Al, this shows that ^{26}Al has been produced no longer than several million years ago and is probably being produced continuously. It is no great extrapolation to argue that nucleosynthesis in general continues in the Galaxy at the present time. Quantitatively, the observations indicate that $^{26}Al/^{27}Al \approx 10^{-5}$ in the interstellar medium. This value averages over the Galactic plane interior to the sun at the present time. This average value was probably much the same when the solar system formed, but the variations in $^{26}Al/^{27}Al$ for various meteoritic inclusions show that there were wide variations in the solar nebula about this value ranging from zero to 10^{-3}.

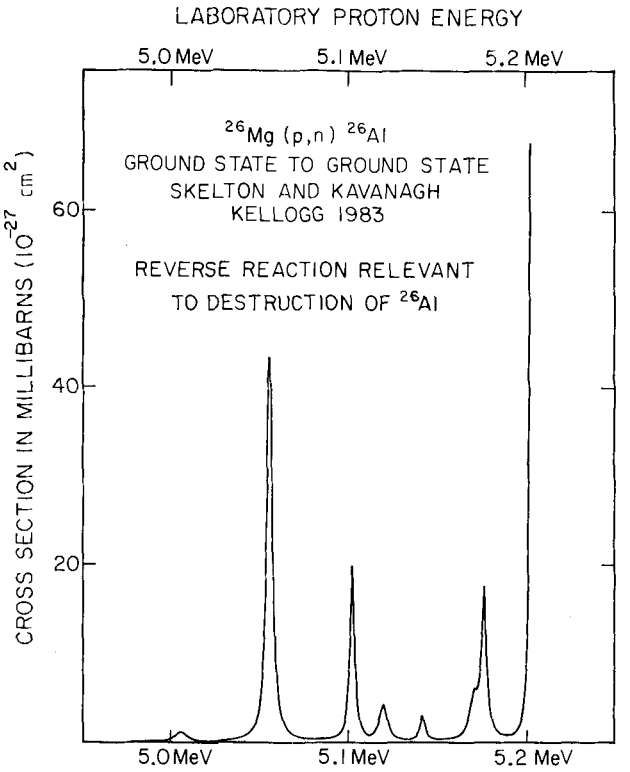

Fig. 22. The cross section in millibarns versus laboratory proton energy for the ground-state to ground-state reaction $^{26}Mg(p,n)^{26}Al$, from *Skelton, Kavanagh,* and *Sargood* [79].

The question immediately arises, what is the site of the synthesis of the ^{26}Al? Since the preparation of reference[52], I have been convinced that ^{26}Al could not be synthesized in supernovae at high temperatures where neutrons are copiously produced because of the expectation of a large cross section for $^{26}Al(n,p)^{26}Mg$. This expectation has been borne out by the measurements on the reverse reaction $^{26}Mg(p,n)^{26}Al$ in the Kellogg Laboratory by *Skelton, Kavanagh,* and *Sargood*[79]. Figure 22 is taken from Figure 1a of these authors and shows the great beauty of high-resolution measurements in experimental Nuclear Astrophysics. Until the ^{26}Al-targets just recently available can be bombarded with neutrons, it is necessary to supplement the laboratory measurements on $^{26}Mg(p,n)^{26}Al$, perforce involving the ground state of ^{26}Mg, with theoretical calculations involving excited states[23], in order to calculate the stellar rate for $^{26}Al(n,p)^{26}Mg$. There is little doubt that this rate is very large indeed.

In [74] and [78] and in *Arnould* et al.[80] it is suggested that ^{26}Al is produced in novae. This is quite reasonable on the basis of nucleosynthesis in novae as discussed by *Truran*[81]. In current models for novae, hydrogen from a binary companion is accreted by a white dwarf until a thermal runaway involving the fast CN-cycle occurs. Similarly, a fast MgAl-cycle may occur with production of $^{26}Al/^{27}Al \gtrsim 1$, as shown in Figure 9 of [52]. The recent experimental measurements cited in [52] substantiate this conclusion. *Clayton*[74] argues that the estimated 40 novae occurring annually in

the Galactic disk can produce the observed $^{26}Al/^{27}Al$ ratio of the order of 10^{-5} on average. He assumes that each nova ejects 10^{-4} $M_\odot$ of material containing a mass fraction of ^{26}Al equal to 3×10^{-4}.

Another possible source of ^{26}Al is spallation induced by irradiation of protoplanetary material by high energy protons from the young sun as it settled on the main sequence. This possibility was discussed very early by *Fowler, Greenstein,* and *Hoyle*[82], who also attempted to produce D, Li, Be and B in this way, requiring such large primary proton and secondary neutron fluxes that many features of the abundance curve in the solar system would have been changed substantially. A more reasonable version of the scenario was presented by *Lee*[83], but without notable success. I find it difficult to believe that an early irradiation produced the anomalies in meteorites. The ^{26}Al in the interstellar medium today certainly cannot have been produced in this way.

Anomalies have been found in the abundances of the stable isotopes of many elements in meteorites compared with in normal solar system material; namely: O, Ne, Mg, Ca, Ti, Kr, Sr, Xe, Ba, Nd, and Sm. The possibility that the oxygen anomalies are non-nuclear in origin has been raised by *Thiemens* and *Heidenreich*[84], but the anomalies in the remaining elements are generally attributed to nuclear processes.

One example is a neutron-capture/beta-decay ($n\beta$) process studied by *Sandler, Koonin,* and *Fowler*[85]. The seed nuclei consisted of all the elements from Si to Cr with normal solar system abundances. When this process operates at neutron densities $\approx 10^7$ mole cm^{-3} and exposure times of $\approx 10^3$ s, small admixtures ($\lesssim 10^{-4}$) of the exotic material produced are sufficient to account for most of the Ca and Ti isotopic anomalies found in the Allende meteorite inclusion EK-1-4-1 by *Niederer, Papanastassiou,* and *Wasserburg*[86]. The anomalies in stable isotope abundances are of the same order as those for short-lived radioactive nuclei and strongly support the view that the solar nebula was inhomogeneous and not completely mixed with regions containing exotic materials up to 10^{-4} or more of normal material.

Agreement for the ^{46}Ca and ^{49}Ti anomalies in EK-1-4-1 was obtained only by increasing the theoretical Hauser-Feshbach cross sections for $^{46}K(n,\gamma)$ and $^{49}Ca(n,\gamma)$ by a factor of 10, on the basis of probable thermal resonances just above threshold in the compound nuclei ^{47}K and ^{50}Ca, respectively. In a CERN report, which subsequently became available, *Huck* et al.[87] reported an excited state in ^{50}Ca just 0.16 MeV above the $^{49}Ca(n,\gamma)$ threshold, which can be produced by *s*-wave capture and fulfills the requirements made in [85].

Reference [85] suggests that the $\approx 10^3$ s exposure time scale is determined by the mean life-time of $^{13}N(\bar{\tau} = 862$ s), produced through $^{12}C(p,\gamma)^{13}N$ by a jet of hydrogen suddenly introduced into the helium burning shell of a Red Giant star where a substantial amount of ^{12}C has been produced by the $3\alpha \rightarrow {}^{12}C$ process. The beta decay $^{13}N(e^+\nu)^{13}C$ is followed by $^{13}C(\alpha,n)^{16}O$ as the source of the neutrons. All of this is very interesting, if true. More to the point, [85] predicts the anomalies to be expected in the isotopes of chromium. Attempts to measure these anomalies are underway now by *Wasserburg* and his colleagues. Again, we shall see!

X. Observational Evidence for Nucleosynthesis in Supernovae

Over the years, there has been considerable controversy concerning elemental abundance observations in the optical wavelength range on Galactic supernovae remnants. To my mind, the most convincing evidence for nucleosynthesis in supernovae has been provided by *Chevalier* and *Kirshner*[88], who obtained quantitative spectral information for several of the fast-moving knots in the supernova remnant Cassiopeia A (approximately dated 1659, but a supernova event was not observed at that time). The knots are considered to be material ejected from various layers of the original star in a highly asymmetric, nonspherical explosion. In one knot, labelled KB33, the following ratios *relative to solar, designated by brackets,* were observed: [S/O] = 61, [Ar/O] = 55, [Ca/O] = 59. It is abundantly clear that oxygen burning to the silicon group elements in the layer in which KB33 originated has depleted oxygen and enhanced the silicon group elements. Other knots and other features designated as filaments show different abundance patterns, albeit, not so easily interpreted. The moral for supernova modelers is that spherically symmetric supernova explosions may be the easiest to calculate but are not to be taken as realistic. Admittedly they have a good answer: it is expensive enough to compute spherically symmetric models. OK, OK!

Most striking of all has been the payoff from the NASA investment in the High Energy Astronomy Observatory (HEAO 2), now called the Einstein Observatory. Using this satellite, *Becker* et al.[89] observed the X-ray spectrum in the range 1 to 4 keV of *Tycho Brahe*'s supernova remnant (1572) shown in Figure 23. An X-ray spectrum is much simpler than an optical spectrum. For me it is wonderful that satellite observations show the K-level X-rays ex-

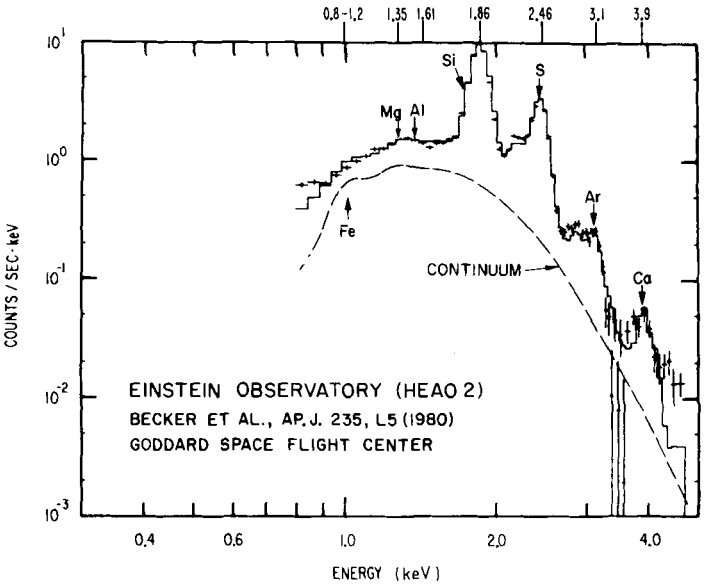

Fig. 23. The Einstein Observatory (HEAO 2) data on the X-ray spectrum of *Tycho Brahe*'s supernova remnant, from *Becker* et al. [89].

pected from Si, S, Ar and Ca just where the Handbook of Chemistry and Physics says they ought to be! Such observations are not all that easy in a terrestrial laboratory.

Shull[90] has used a single-velocity, non-ionization-equilibrium model of a supernova blast-wave to calculate abundances in *Tycho*'s remnant *relative to solar, designated by brackets,* and finds: [Si]=7.6, [S]=6.5, [Ar]=3.2 and [Ca]=2.6. With considerably greater uncertainty, he gives [Mg]=2.0 and [Fe]=2.1. He finds different enhancements in *Kepler*'s remnant (1604) and in Cassiopeia A. One more lesson for the modelers: no two supernovae are alike. Nucleosynthesis in supernovae depends on their initial mass, rotation, mass-loss during the Red Giant stage, the degree of symmetry during explosion, initial heavy element content, and probably other factors. These details aside, it seems clear that supernovae produce enhancements in elemental abundances up to iron and probably beyond. Detection of the much rarer elements beyond iron will require more sensitive X-ray detectors operating at higher energies. The nuclear debris of supernovae eventually enriches the interstellar medium from which succeeding generations of stars are formed. It becomes increasingly clear that novae also enrich the interstellar medium. Sorting out these two contributions poses interesting problems in ongoing research in all aspects of Nuclear Astrophysics.

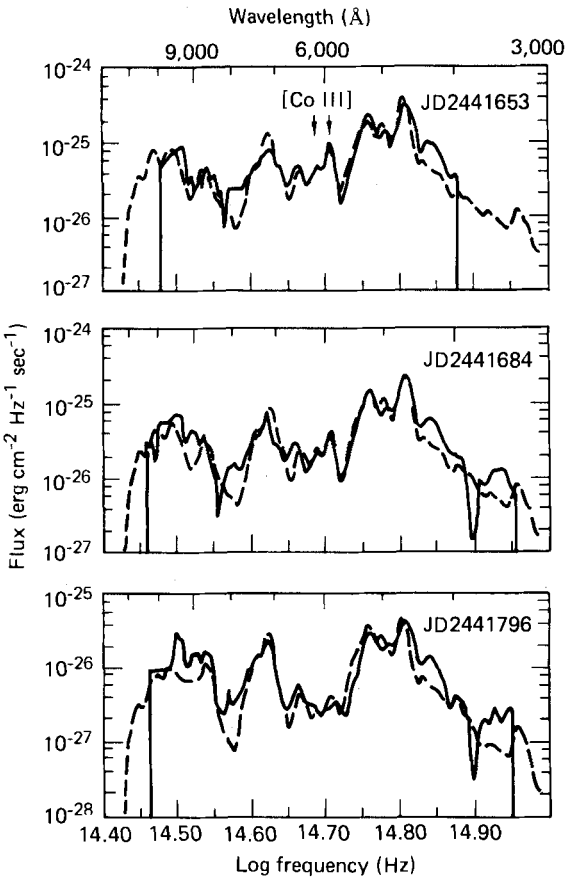

Fig. 24. Analysis by *Axelrod* [91], yielding two emission lines from Co^{III} in the observations on SN 1972e obtained by *Kirshner* and *Oke* [92]. The observations were made 233, 264 and 376 days after JD2441420, assigned as the initial day of the supernova explosion. The mean lifetime of ^{56}Co is 114 days; the Co^{III} lines appear to decay in keeping with their emission from radioactive ^{56}Co.

Explosive silicon burning in the shell just outside a collapsing supernova core primarily produces ^{56}Ni, as shown in Figure 16. It is generally believed that the initial energy source for the light curves of type I supernovae is electron capture by ^{56}Ni ($\bar{\tau}=8.80$ days) to the excited state of ^{56}Co at 1.720 MeV, with subsequent gamma ray cascades to the ground state. These gamma rays are absorbed and provide energy to the ejected envelope. The subsequent source of energy is electron capture and positron emission by ^{56}Co ($\bar{\tau}=114$ days) to a number of excited states of ^{56}Fe, with gamma ray cascades to the stable ground state of ^{56}Fe. Both the positrons and the gamma rays heat the ejected material. If ^{56}Co is an energy source, there should be spectral evidence for cobalt in newly discovered Type I supernovae, since its lifetime is long enough for detailed observations to be possible after the initial discovery.

The cobalt has been observed! *Axelrod*[91] studied the optical spectra of SN1972e obtained by *Kirshner* and *Oke*[92]. The spectra obtained at 233, 264, and 376, days after Julian day 2441420, assigned as the initial day of the explosive event, are shown in Figure 24. *Axelrod* assigned the two emission lines near 6000 Å ($\log v=14.7$) to Co^{III}. They are clearly evident at 233 and 264 days, but are only marginally evident at 376 days ($\approx\bar{\tau}$). The lines decay in reasonable agreement with the mean lifetime of ^{56}Co.

Branch et al.[93] have studied absorption spectra obtained during the first hundred days of SN1981b. Their results at maximum light are shown in the top curve of Figure 25. Using the carbon deflagration model for Type I supernovae of *Nomoto*[67], *Branch*[94] has calculated the spectrum shown in the lower curve of Figure 25. Deep absorption lines of Co^{II} are clearly evident near 3300 and 4000 Å.

It is my conclusion that there is substantial evidence for nucleosynthesis in supernovae of elements produced in oxygen and silicon burning. The role of neutron capture processes in supernovae will be discussed in the next section.

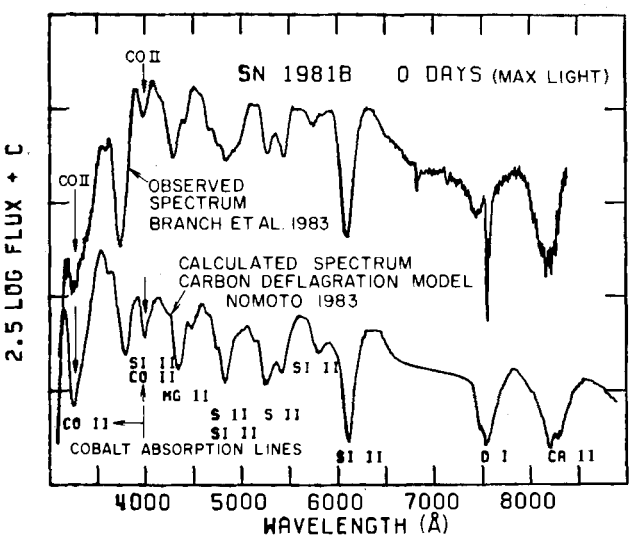

Fig. 25. Top: Analysis by *Branch* et al. [93] of their absorption spectrum of SN 1981b at maximum light showing evidence for Co^{II} absorption features. Bottom: Comparison with the calculated spectrum expected from the carbon deflagration model for Type I supernovae, according to the calculations of *Nomoto* [67].

XI. Neutron Capture Processes in Nucleosynthesis

In Section I the need for two neutron capture processes for nucleosynthesis beyond $A \gtrsim 60$ was discussed in terms of early historical developments in Nuclear Astrophysics. These two processes were designated the *s*-process, for neutron capture slow (*s*) compared to electron beta-decay, and the *r*-process, for neutron capture rapid (*r*) compared to electron beta-decay in the process networks.

For a given element, the heavier isotopes are frequently by-passed in the *s*-process and are produced only in the *r*-process; thus, the designation *r*-only. Lighter isotopes are frequently shielded by more neutron-rich stable isobars in the *r*-process and are produced only in the *s*-process; thus, the designation s-only. The lightest isotopes are frequently very rare because they are not produced in either the *s*-process or the *r*-process and are thought to be produced in what is called the *p*-process. The *p*-process involves positron production and capture, proton-capture, neutron-photoproduction, and/or (p,n)-reactions and will not be discussed further. The reader is referred to *Audouze* and *Vauclair*[95]. The results of the *s*-process, the *r*-process, and the *p*-process are frequently illustrated by reference to the ten stable isotopes of tin. The reader is referred to Figures 10 and 11 of the first reference in [96].

It is fair to say that the *s*-process has the clearest phenomenological basis of all processes of nucleosynthesis. This is primarily the result of the correlation of *s*-process abundances, first delineated by *Seeger, Fowler,* and *Clayton*[97], with the beautiful series of measurements on neutron capture cross sections in the 1 to 100 keV range carried out at the Oak Ridge National Laboratory group under *Macklin* and *Gibbons*[98].

The correlation is illustrated in Figure 26, which shows the product of neutron capture cross sections (σ) at 30 keV multiplied by *s*-process abundances (N) as a function of atomic mass for *s*-only nuclei and those produced predominately by the *s*-process. It is not difficult to understand in first-order approximation that the product σN should be constant in the *s*-process synthesis. A nucleus with a small (large) neutron capture cross-section must have a large (small) abundance to maintain continuity in the *s*-capture path. Figure 26 demonstrates this in the *plateaus* shown from $A = 90$ to 140 and from $A = 140$ to 206. The anomalous behavior below $A = 80$ is discussed in *Almeida* and *Käppeler*[99], from which Figure 26 is taken.

Nuclear shell structure introduces the *precipices* shown in Figure 26 at $A \approx 84$, $A \approx 138$, and $A \approx 208$, which correspond to the *s*-process abundance peaks in Figure 2. At these values of A, the neutron numbers are "magic", $N = 50$, 82, and 126. The cross sections for neutron capture into new neutron shells are very small at these magic numbers. With a finite supply of neutrons, it follows that the product σN must drop to a new plateau, just as is observed. Quantitative explanations of this effect have been given by *Ulrich*[100] and by *Clayton* and *Ward*[101].

What is the site of the *s*-process, and what is the source of the neutrons? A very convincing answer has been given by *Iben*[102] that the site is the He-burning shell of a pulsating Red Giant with the $^{22}Ne(\alpha,n)^{25}Mg$ reaction as the neutron source. Critical discussions have been given by *Almeida* and *Käppeler*[99] and by *Truran*[103]. The latter reference reserves the possibility that the $^{13}C(\alpha,n)^{16}O$ reaction is the neutron source.

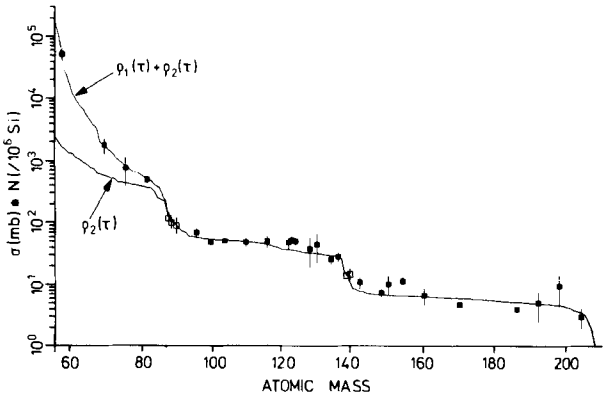

Fig. 26. Neutron capture cross section at 30 keV in millibarns multiplied by solar system abundances relative to Si = 10^6 versus atomic mass for nuclei produced in the s-process from *Almeida* and *Käppeler* [99]. Theoretical calculations are shown for a single exponential distribution, in neutron exposure, τ, $\rho_2(\tau)$, and for two such distributions $\rho_1(\tau)+\rho_2(\tau)$.

We turn now to the *r*-process. This process has been customarily treated by the *waiting point* method of B^2FH[18]. Under explosive conditions, a large flux of neutrons drives nuclear seeds to the neutron-rich side of the valley of stability where, depending on the temperature, the (n,γ)-reaction and the (γ,n)-reaction reach equality. The nuclei wait at this point until electron beta-decay transforms neutrons in the nuclei into protons, whence further neutron capture can occur. At the cessation of the *r*-process, the neutron-rich nuclei decay to their stable isobars. In the first order, this means that the abundance of an *r*-process nucleus multiplied by the electron beta-decay rate of its neutron rich *r*-process isobar progenitor will be roughly constant. At magic neutron numbers in the neutron-rich progenitors, beta-decay must perforce open the closed neutron shell in transforming a neutron into a proton and there the rate will be relatively small. Accordingly, the abundance of progenitors with $N = 50$, 82, and 126 will be large. The associated number of protons will be less than in the corresponding *s*-process nuclei with a magic number of neutrons. It follows that the stable daughter isobars will have smaller mass numbers, and this is indeed the case, the *r*-process abundance peaks occurring at $A \approx 80$, $A \approx 130$, and $A \approx 195$—all below the corresponding s-process peaks, as illustrated in Figure 2.

A phenomenological correlation of *r*-process abundances with beta-decay rates made by *Becker* and *Fowler*[104] and a detailed illustration of this correlation between solar system *r*-process abundances and theory are given in Figure 13 of the first reference in [96]. It is too phenomenological to satisfy critical nuclear astrophysicists. They wish to know the site of the high neutron fluxes demanded for *r*-process nucleosynthesis and the details of the *r*-process path through nuclei far from the line of beta-stability.

There is also general belief at the present time that the waiting point approximation is a poor one and must be replaced by dynamical *r*-process flow calculations taking into account explicit (n,γ), (γ,n) and beta-decay rates with time-varying temperature and neutron flux. *Schramm*[105]

has discussed such calculations in some detail and has emphasized that nonequilibrium effects are particularly important during the freeze-out at the end of the *r*-process when the temperature drops and the neutron flux falls to zero.

Simple dynamical calculations have been made by *Blake* and *Schramm*[106] for a process they designated as the *n*-process, and by *Sandler, Fowler,* and *Koonin*[85] for their *nβ*-process discussed in Section IX. The most ambitious calculations have been made by *Cameron, Cowan,* and *Truran*[107]. This paper gives references to their previous herculean efforts in dynamical *r*-process calculations. An example of their results is shown in Figure 27. They emphasize that they have not been able to find a plausible astrophysical scenario for the initial ambient conditions required for Figure 27. In spite of this, I am convinced that they are on the right track to an eventual understanding of the dynamics and site of the *r*-process.

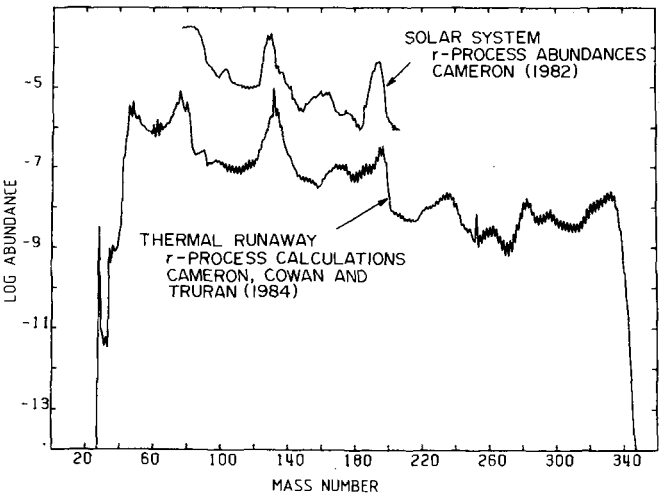

Fig. 27. Abundances produced in the *r*-process versus atomic mass number in the thermal runaway model (lower curve) of *Cameron, Cowan,* and *Truran* [107] compared with the solar system *r*-process abundances (upper curve) of *Cameron* [3].

Many suggestions have been made for possible sites of the *r*-process, almost all in supernovae explosions where the basic requirement of a large neutron flux of short duration is met. These suggestions are reviewed by *Schramm*[105] and *Truran*[103]. To my mind, the helium-core, thermal runaway *r*-process of *Cameron, Cowan,* and *Truran*[107] is the most promising. These authors do not rule out the $^{22}Ne(\alpha,n)^{25}Mg$ reactions as the source of the neutrons, but their detailed results shown in Figure 27 are based on the $^{13}C(\alpha,n)^{16}O$ reaction as the source. They start with a star formed from material with the same heavy-element abundance distribution as in the solar system but with smaller total amount. They assume a significant amount of ^{13}C in the helium core of the star after hydrogen burning. This ^{13}C was produced previously by the introduction of hydrogen into the core which had already burned half of its helium into ^{12}C. For Figure 27, they assume a ^{13}C abundance of 14.3 percent by mass, density equal to 10^6 gm cm^{-3}, and an initial temperature of 1.6×10^8 K, which is raised by the initial slow ^{13}C-burning to an eventual maximum of 3.6×10^8 K. The electrons in the core are initially degenerate but the rise in temperature lifts the degeneracy, producing a thermal runaway with expansion and subsequent cooling of the core. This event is the second helium-flash episode in the history of the core and, if it occurs, only a small amount of the *r*-process material produced need escape into the interstellar medium to contribute the *r*-process abundance in solar system material. It is my belief that a realistic astrophysical site for the thermal runaway, perhaps with different initial conditions, will be found. I rest the case.

XII. Nucleocosmochronology

Armed with their *r*-process calculations of the abundances of the long-lived parents of the natural radioactive series ^{232}Th, ^{235}U, and ^{238}U and with the then current solar system abundances of these nuclei, B^2FH[18] were able to determine the duration of *r*-process nucleosynthesis from its beginning in the first stars in the Galaxy up to the last events before the formation of the solar system. The general idea was originally suggested by *Rutherford*[108]. B^2FH[18] made a major advance by taking into account the contributions to the abundance of the long-lived *eon glasses* from the decay of their short-lived progenitors also produced in the *r*-process. The parents of the natural radioactive series are indeed excellent *eon glasses* with their mean lifetimes: ^{232}Th, 20.0×10^9 years; ^{238}U, 6.51×10^9 years; ^{235}U, 1.03×10^9 years. The analogy with *hour glasses* is fairly good; the sand in the top of the *hours glass* is the radioactive parent, that in the bottom is the daughter. The analogy fails in that in the *eon glasses* "sand" (Th, U) is being added or removed, top and bottom, by nucleosynthesis (production in stars) and astration (destruction in stars). Properly expressed differential equations can compensate for this failure.

The abundances used were those observed in meteorites assumed to be closed systems since their formation, taken to have occurred 4.55 billion years ago. It was necessary to correct for free decay during this period to obtain abundances for comparison with calculations based on *r*-process production plus decay over the duration of Galactic nucleosynthesis before the meteorites became closed systems. Fortunately, ratios of abundances, $^{232}Th/^{238}U$ and $^{235}U/^{238}U$, sufficed since absolute abundances could not, and still cannot, be calculated with the necessary precision. The calculations required only the elemental ratio Th/U in meteorites since the isotopic ratio $^{235}U/^{238}U$ was assumed to be the same for meteoritic and terrestrial samples. The Apollo Program has added lunar data to the meteoritic and terrestrial in recent years.

B^2FH[18] considered a number of possible models, one of which assumed *r*-process nucleosynthesis *uniform* in time and an arbitrary time interval between the last *r*-process contribution to the material of the solar nebula and the closure of the meteorite systems. A zero value for this time interval indicated that the production of uranium started 18 billion years ago. When this time interval was taken to be 0.5 billion years, the production started 11.5 billion years ago. These values are in remarkable, if coincidental, concordance with current values.

It is appropriate to indicate at this point that nucleocosmochronology yields, with additional assumptions, an estimate for the age of the expanding Universe completely independent of red shift-distance observations in astronomy on distant galaxies. The assumptions referred to in the previous sentence are that the *r*-process started soon, less than a billion years, after the formation of the Galaxy, and that the Galaxy formed soon, less than a billion years, after the "big bang" origin of the Universe. Addition of a billion years or so to the start of *r*-process nucleosynthesis yields an independent value, based on radioactivity, for the age or time back to the origin of the expanding Universe.

Much has transpired over the recent years in the field of nucleocosmochronology. I have kept my hand in most recently in [109]. Exponentially decreasing nucleosynthesis with the time constant in the negative exponent a free parameter to be determined by the observed abundance ratios along with the duration of nucleosynthesis was introduced by *Fowler* and *Hoyle*[110]. For the time constant in the denominator of the exponent set to infinity, uniform synthesis results. When it is set to zero, a single spike of synthesis results. With two observed ratios, two free parameters in a model can be determined. As time went on, the ratios $^{129}I/^{127}I$ and $^{244}Pu/^{238}U$ with $\bar{\tau}(^{129}I) = 0.023 \times 10^9$ years and $\bar{\tau}(^{244}Pu) = 0.117 \times 10^9$ years were added to nucleocosmochronology to permit the determination of two additional free parameters, the arbitrary time interval of B^2FH[18] previously discussed and the fraction of *r*-process nucleosynthesis produced in a last gasp "spike" at the end of the exponential time dependence.

Sophisticated models of Galactic evolution were introduced by *Tinsley*[111]. A method for model-independent determinations of the mean age of nuclear chronometers at the time of solar system formation was developed by *Schramm* and *Wasserburg*[112]. In this method, the mean age is one-half the duration for uniform synthesis and is equal to the actual time of single-spike nucleosynthesis. This indicates that one can expect no more than a range of a factor of two in the time back to the beginning of nucleosynthesis in widely different models for its time variation. These developments are reviewed by *Schramm*[105].

The most recent calculations are those of *Thielemann, Metzinger,* and *Klapdor*[113]. Their results, revised by his own most recent calculations, are shown in Figure 28, prepared by *F.-K. Thielemann*. The pre-solar spike and its time of occurrence before the meteorites became closed systems depend primarily on the *minute glasses,* ^{129}I and ^{244}Pu. The *eon glasses,* $^{232}Th/^{238}U$ and $^{235}U/^{238}U$, indicate that *r*-process nucleosynthesis in the Galaxy started 17.9 billion years ago, with uncertainties of $+2$ billion years and -4 billion years according to [113]. This value is to be compared with my value of 10.5 ± 2.3 billion years ago given in [109]. Inputs of production and final abundance ratios have changed[113]! *Thielemann* and I are now recomputing the new value for the duration using an initial spike in Galactic synthesis plus uniform synthesis thereafter.

Reference[113] indicates that the age of the expanding Universe is 19 billion years, give or take several billion years. This is to be compared to the Hubble time or reciprocal of Hubble's constant given by *Sandage* and *Tammann*[114] as 19.5 ± 3 billion years. However, the Hubble

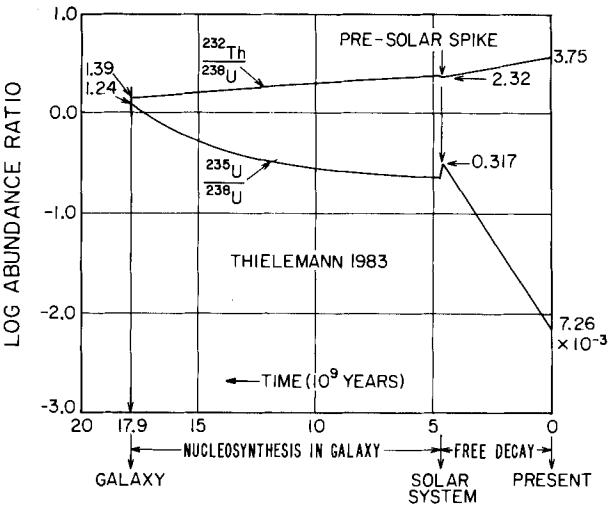

Fig. 28. The abundance ratios for $^{232}Th/^{238}U$ and for $^{235}U/^{238}U$ produced by theoretical *r*-process nucleosynthesis over the lifetime of the Galaxy prior to the formation of the solar system, from *Thielemann, Metzinger,* and *Klapdor* [113]. The free decays over the lifetime of the solar system to reach the present values for these ratios, $(^{232}Th/^{238}U)_0 = 3.75$ and $(^{235}U/^{238}U)_0 = 7.26 \times 10^{-3}$ are also shown. The production ratios in each *r*-process event was theoretically calculated to be 1.39 for $^{232}Th/^{238}U$ and 1.24 for $^{235}U/^{238}U$. Compare with Figure 10 in first reference under [109].

time is equal to the age of the expanding Universe only for a completely open Universe with mean matter density much less than the critical density for closure, which can be calculated from the value for the Hubble time just given to be 7×10^{-30} g cm^{-3}. The observed visible matter in galaxies is estimated to be ten percent of this, which reduces the age of the Universe to 16.5 billions years. Invisible matter, neutrinos, black holes, etc. may add to the gravitational forces which decrease the velocity of expansion and may thus decrease the age to that corresponding to critical density, which is 11.1 billion years. If the expansion velocity was greater in the past, the time to the present radius of the Universe is correspondingly less. Moreover, there are those who obtain results for the Hubble time equal to about one-half that of *Sandage* and *Tammann*[114], as reviewed in *van den Bergh*[115]. There is much to be done on all fronts!

A completely independent nuclear chronology involving the radiogenic ^{187}Os produced during Galactic nucleosynthesis by the decay of ^{187}Re ($\bar{\tau} = 65 \times 10^9$ years) was suggested by *Clayton*[116]. *Schramm*[105] discusses still other chronometric pairs. *Clayton*'s suggestion involves the *s*-process, even though the ^{187}Re is produced in the *r*-process. It requires that the abundance of ^{187}Re, the parent, be compared to that of its daughter, ^{187}Os, when the *s*-only production of this daughter nucleus is substracted from its total solar system abundance. This was to be done by comparing the neutron capture cross section of ^{187}Os with that of its neighboring *s*-only isotope ^{186}Os, which does not have a longlived radioactive parent, and using the $N\sigma = constant$ rule for the *s*-process.

Fowler[117] threw a monkey wrench into the works by pointing out that ^{187}Os has a low-lying excited state at 9.75 keV which is practically fully populated at $kt = 30$ keV, corresponding to the temperature $T = 3.5 \times 10^8$ K, at which the *s*-process is customarily assumed to occur. Moreover with

spin $J=3/2$ this state has twice the statistical weight $(2J+1)$ of the ground state with spin $J=1/2$. Measurements of the ground state neutron-capture cross-section yields only one-third of what one needs to know.

All of this has led to a series of beautiful and difficult measurements for neutron-induced reactions on the isotopes of osmium. *Winters* and *Macklin*[118] found the Maxwell-Boltzmann average ground state (laboratory) cross-section ratio for $^{186}Os(n,\gamma)$ relative to that for $^{187}Os(n,\gamma)$ to be 0.478 ± 0.022 at $kT=30$ keV with a slow dependence on temperature. This ratio must be multiplied by a theoretical factor to correct the ^{187}Os cross section in the denominator of the cross-section ratio for that of its excited state. The larger the theoretical ^{187}Os excited state capture, the smaller this factor. *Woosley* and *Fowler*[119] used Hauser-Feshbach theory to give an estimate for this factor in the range 0.8 to 1.10, which is little comfort because it multiplies one number comparable to the number from which it must be subtracted. These factors translated into a time for the beginning of the *r*-process in the Galaxy in the range 14 to 19 billion years. In despiration, I suggested privately that inelastic neutron scattering off the ground state of ^{187}Os to its excited state at 9.75 keV might yield information on the properties of the excited state. Measurements by *Macklin* et al.[120] and *Hershberger* et al.[121] determined these inelastic neutron scattering cross sections, which yielded inherent support of the lower value of the *Woosley* and *Fowler*[119] factor and thus a greater value for the time back to the beginning of *r*-process nucleosynthesis on the 18 to 20 billion year range. It has to be admitted that this is concordant with the latest value from the Th/U-nucleocosmochronology.

Once again in despiration I privately suggested that measurement of the neutron capture cross section on the ground state of ^{189}Os might be helpful. In ^{189}Os the ground state has the same spin and Nilsson numbers as the excited state of ^{187}Os and an excited state corresponding to the ground state of ^{187}Os. Measurements by *Browne* and *Berman*[122] are available but are now being checked by an Oak Ridge National Laboratory, Denison University and University of Kentucky consortium.

It will be clear that the lifetime of ^{187}Re comes directly into the calculations under discussion. There has been some discrepancy in the past between lifetimes measured geochemically and those measured directly by counting the electrons emitted in the 2.6 keV decay $^{187}Re(e^-\nu)^{187}Os$. Direct measurement yields only the lifetime for electron-emission to the continuum, while geochemistry yields the lifetime for electron-emission both to the continuum and to bound states in ^{187}Os. The entire matter is treated in considerable theoretical detail by *Williams, Fowler,* and *Koonin*[123], who found that the bound-state decay is negligible and that the direct measurements by *Payne* and *Drever*[124], which agree with the geochemical measurements of *Hirt* et al.[125], are correct.

There is also the vexing problem of the possible decrease in the effective lifetime of ^{187}Re in the Galactic environment. The ^{187}Re included in the material of the interstellar medium which forms new stars is subject to destruction by the *s*-process (astration) as well as being produced by the *r*-process. This decreases the effective lifetime of the ^{187}Re and all chronometric times based on the Re/Os chronology. This problem is discussed in elaborate detail by *Yokoi, Takahashi,* and *Arnould*[126]. The time back to the beginning of *r*-process nucleosynthesis could be as low as 12 billion years. It is appropriate to end this last section before the concluding section with considerable uncertainty in nucleocosmochronology indicating that, as in all nuclear astrophysics, there is much exciting experimental and theoretical work to be done for many years to come. Amen!

XIII. Conclusion

In spite of the past and current researches in experimental and theoretical Nuclear Astrophysics, illustrated in what I have just shown you, the ultimate goal of the field has not been attained. *Hoyle*'s grand concept of element synthesis in the stars will not be truly established until we attain a deeper and more precise understanding of many nuclear processes operating in astrophysical environments. Hard work must continue on all aspects of the cycle: experiment, theory, observation. It is not just a matter of filling in the details. There are puzzles and problems in each part of the cycle which challenge the basic ideas underlying nucleosynthesis in stars. Not to worry—that is what makes the field active, exciting and fun! It is a great source of satisfaction to me that the Kellogg Laboratory continues to play a leading role in experimental and theoretical Nuclear Astrophysics.

And now permit me to pass along one final thought in concluding my lecture. My major theme has been that all of the heavy elements from carbon to uranium have been synthesized in stars. Let me remind you that your bodies consist for the most part of these heavy elements. Apart from hydrogen you are 65 percent oxygen and 18 percent carbon with smaller percentages of nitrogen, sodium, magnesium, phosphorus, sulphur, chlorine, potassium, and traces of still heavier elements. Thus it is possible to say that you and your neighbor and I, each one of us and all of us, are truly and literally a little bit of stardust.

Charles Christian Lauritsen taught me a Swedish toast. I conclude with this toast to my Swedish friends: "*Din skål, min skål, alla vackra flickor skål. Skål!*"

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Modelling the Chemistry of Zeolites by Computer Graphics**

By Subramaniam Ramdas, John M. Thomas*, Paul W. Betteridge, Anthony K. Cheetham, and E. Keith Davies

The unique structural, adsorptive, and catalytic properties of zeolites are particularly amenable to illustration by computer (especially color) graphics. The siting of cations, the accommodation of guest reactant or product species, as well as the occurrence of various kinds of intergrowths (e.g. twin planes and coincidence boundaries) within these microporous solids can all be effectively portrayed by graphical means in such a manner as to emphasize the shape-selective character of the host zeolite. The dynamics of translational and angular motion of guest species (for example benzene) in a channel of molecular dimensions within a typical zeolitic solid (for example silicalite) can also be probed interactively using appropriate potential functions.

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[**] The defect structure simulations outlined in Section 3 were displayed on a Sigma 5684 raster graphics terminal linked to an IBM 3081 computer, using locally written routines. The calculations described in Section 4 were carried out using the CHEMGRAF suite of programs on a VAX 11/750 computer (E. K. Davies: CHEMGRAF User Manual, Chemical Crystallography Laboratory, University of Oxford, Oxford, UK 1984). A Sigma 5688 raster graphics terminal was used to display the results, which were photographed directly from the terminal.

1. Introduction

Zeolites were discovered more than two hundred years ago. They have been used for decades as water softeners and cation exchangers, as well as vehicles for the separation of molecules according to shape and size. In addition to their use as molecular sieves, they have, since the mid-sixties, been extensively employed as industrial catalysts[1], and, of late, highly siliceous variants of zeolites have led to important new developments in shape-selective heterogeneous catalysis[2].

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Zeolites can be described by the general formula $M_{x/n}[(AlO_2)_x(SiO_2)_y]\cdot m\,H_2O$, where the cations M of valence n neutralize the charges on the aluminosilicate framework, which in turn is composed of corner-sharing SiO_4 and AlO_4 tetrahedra. The linkages between these units generate cages or pores of molecular dimensions (3 to 8 Å in diameter). Their surface area, which lies largely within the bulk, is typically 500 $m^2\,g^{-1}$. The neutralizing cations are located in more or less well defined sites in the various cavities that exist within the structure, and the water molecules fill up the voids; the water can be expelled upon heating and evacuation. In view of their exceptional porosity, the process of cation exchange in zeolites takes place very readily. Likewise, they permit facile movement of small neutral molecules into or out of the bulk structure. By adjusting the valency and the size of the exchangeable cation, the sieving and separation processes can, as it were, be fine tuned[3]. Moreover, by increasing the silicon to aluminum ratio of the macro-anionic framework by dealumination[4], the microporosity can be further enhanced. Introduction of hydrocarbons is easier when the Si/Al ratio of the dehydrated framework is higher, not only because there are fewer exchangeable cations but also because the framework itself becomes progressively more hydrophobic (i.e. more oleophilic) as aluminum is eliminated. A further advantage possessed by these structures is that Brønsted acid sites, one type of which may be rather crudely represented as

are distributed quite uniformly throughout the structure. These are active sites for many catalytic reactions involving hydrocarbons; and since they are situated at internal surfaces accessible to reactant species, many subtle, shape-selective chemical conversions can be carried out using zeolitic catalysts.

In order to understand all the various nuances of structural chemistry exhibited by zeolites, it is often essential to construct appropriate models which, inter alia, emphasize the framework topology and the shapes and sizes of the cavities and tunnels. A beautiful illustration of such models of some of the zeolites has been shown by *Sten Andersson* in his review on the description of complex inorganic crystal structures[5]. Although such models are invaluable for visual comprehension, their construction is usually time consuming and they often have real limitations. For example, a satisfactory representation of the extra-framework cations is difficult using conventional modelling techniques, but the chemistry of zeolites is intimately linked with the locations of these ions. This is one respect in which computer graphics can play a useful role. But we can go much further than merely providing effective illustrations for the understanding of structures. A computer model can readily be manipulated to permit examination of various structural features; for instance, the locations of the cations can be rearranged, suspected order-disorder phenomena in the cation sublattice can be monitored, and defects of various kinds can be introduced. Furthermore, calculations of the interaction energies can be performed, provided suitable theoretical models exist, to monitor the energetics of various operations that simulate the physicochemical aspects of adsorption, diffusion, etc. For example, interaction energies between the zeolite framework and a guest molecule can be investigated using such procedures. We shall describe computer simulations that combine a facility for carrying out "experiments" (some of which are, as yet, impossible with real substances) with a powerful method for displaying and evaluating the results. The possibilities of computer modelling and graphics have been nicely appreciated in other areas of chemistry. For example, in the last few years, pharmacologists have been quick to capitalize on the scope and utility of these techniques in the design of drugs[6a] and other biologically important materials[6b].

In this paper, we provide an introduction to the application of computer graphics to the study of some problems in zeolite chemistry, and in so doing we outline some of the more significant results obtained to date. Three aspects of computer graphics are emphasized:

1. The provision of clear illustrations depicting many features of zeolitic structures determined by X-ray studies.
2. More sophisticated applications, such as the modelling of possible intergrowths, twinning, and other planar faults of the kind commonly encountered among zeolites.
3. Dynamic simulation of interactions between organic molecules and the framework.

Such studies provide novel and convenient methods for probing the behavior of zeolitic catalysts under conditions quite close to those used in catalytic reactions. Although we will give typical examples of reactant and product shape-selectivity, we expect that suitable extension of these techniques will allow one to investigate even the "transition state" selectivity of reaction intermediates[7], in real time.

2. Color Illustrations of Zeolite Frameworks

2.1. Zeolites X and Y

Zeolites X and Y are structurally analogous to the mineral faujasite. The building units are truncated octahedra, also known as sodalite cages, β-cages, or tetrakaidecahedra (the three terms are synonymous), which are linked to adjacent cages via hexagonal biprisms, thereby yielding larger "supercages", also known as α-cages (Fig. 1). The principal sites for the extra-framework cations are known as the S(I), S(I′), S(II), and S(II′) sites. The Si–O–Al framework and the locations of the principal cation sites are shown in Figure 1, from which we can readily grasp the significance of the occupancy factors reported for the various sites. The features to be noted are: (i) adjacent S(I) and S(I′) sites are not simultaneously occupied by cations, whereas almost all the S(II) sites in the wall of the supercage are occupied; (ii) cations preferring higher coordination numbers usually occupy the S(I) sites. The tetrahedral

clustering of S(II′) sites within the β-cage precludes any significant occupancy.

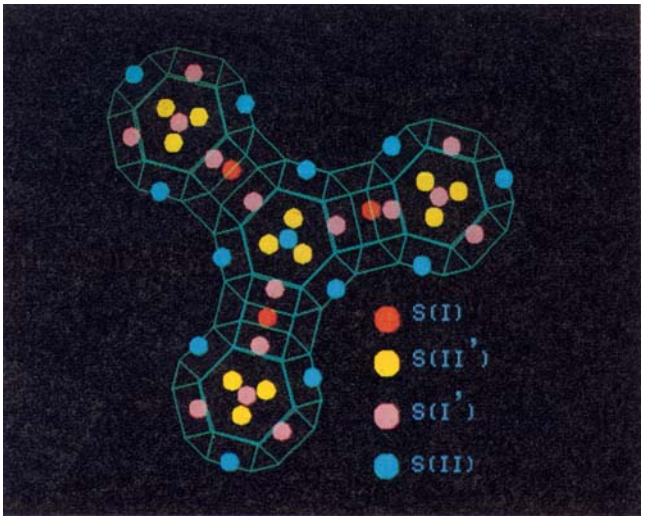

Fig. 1. Faujasite framework (oxygens not shown) with principal cation sites. Whereas, sites S(I′) and S(II′) are within the β-cages, S(I) and S(II) are in the hexagonal biprisms and the supercages, respectively. In addition, there are cation sites which are also known to be in the supercages.

New methods of achieving the isomorphous replacement of aluminum by silicon[4] have made it possible to render a zeolite cavity or channel relatively free from cations. As mentioned earlier, this changes the zeolite's affinity towards neutral organic molecules by increasing the free space available and also by enlarging the channel size; there is also a reduction in the polarity of the zeolite. As a typical example, in Figure 2 (top) we show an ethane molecule within the supercage in zeolite Y. The 12-membered ring entrance to the α-cage is wide enough to accommodate a large organic molecule, for example azoisobutyronitrile (AIBN). The introduction of molecules like AIBN is interesting because of the possible photogeneration of radicals[8] that recombine to yield the tetramethyl dinitrile with loss of N_2. Preferential formation of this product over other unsymmetrical ones[9] is a possibility because of the restricted rotation and translation of the trapped radicals within the supercage. This is reflected in Figure 2 (bottom), where the least squares best plane projection of AIBN gives a maximum "van der Waals length" of 8.9 Å, which is within the diameter of the supercage (9.2 Å). Also, the "maximum overlap projection" of the molecule has a diameter of 6.2 Å, well within the 7 Å aperture (shown in Figure 2b).

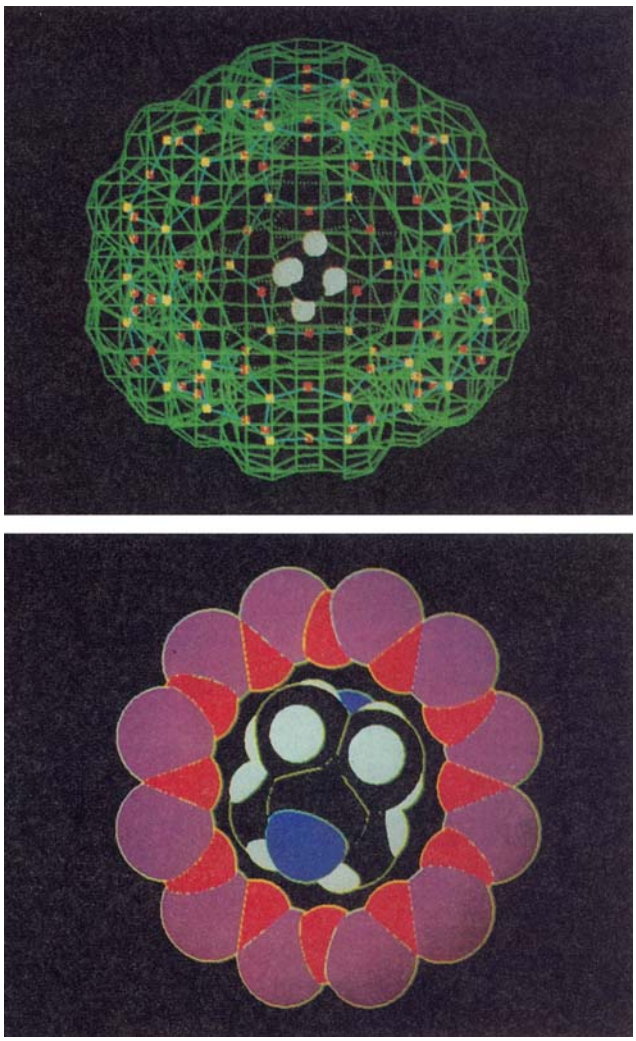

Fig. 2. The molecules, (top) ethane and (bottom) azoisobutyronitrile within the supercage of the faujasitic framework. For clarity, the twelve-membered ring opening to the supercage is alone shown in the bottom picture, with Si and O colored in magenta and red (in their van der Waals radii), respectively.

2.2. Zeolites A and ZK-4

The structure of zeolite A is also made up of connected sodalite cages, but in this case the tetrakaidecahedra are linked via cubes rather than hexagonal prisms. The locations of the extra-framework cations in the $K^{\oplus}$-form[10] of zeolite A are shown in Figure 3. This clearly shows that the 'blue' cations occupy most of the centers of the six-membered rings (O atoms (red) not counted), slightly altering the kinetic diameter of the channels and reducing the free volume of the supercage. In addition, the large "blue" cations block the eight-membered ring channels. One way of altering the zeolite to allow hydrocarbon molecules to diffuse through is to replace the monovalent cation by a divalent ion such as strontium. Not only is the number of ions required to neutralize the framework charge halved, but also the remaining ions tend to occupy the sites in the six-membered ring windows leaving the channels free. Alternatively, and preferably, one may increase the silicon to aluminum ratio, as in the zeolite ZK-4, which has a framework structure the same as that of zeolite A but with a Si/Al ratio of at least 2.5. Zeolite ZK-4, therefore, requires fewer cations than zeolite A to balance framework charge, leading to freer channels. A straight chain hydrocarbon can diffuse relatively freely through such channels.

This shape-selectivity of zeolites for some reactant and product molecules, which is responsible for their novel catalytic role, rivaling that of certain enzymes, can be proved effectively with computer graphics. In Figure 4 we show

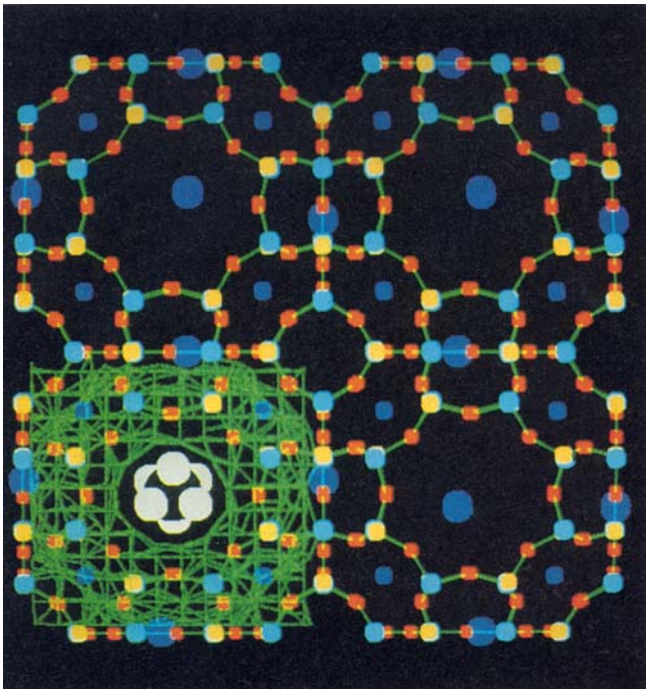

Fig. 3. The framework and the cations in the $K^{\oplus}$-form of zeolite A. Red: O, yellow/light blue: Si/Al, dark blue (small and large): cation sites. The network covering the van der Waals surface is shown, with a molecule of ethane in the channel. To permit adsorption and diffusion of this molecule, the $K^{\oplus}$ ions blocking the eight-membered rings must be removed. This is effected either by increasing the Si/Al ratio (thereby decreasing the number of exchangeable cations per unit-cell, as in ZK-4) or, for a fixed Si/Al ratio, by replacement of monovalent by divalent ions.

the ease with which a methanol molecule can diffuse through the straight channels of the zeolite ZSM-5, yielding products including *n*-alkanes in the gasoline range. On the other hand, branched hydrocarbons are trapped inside the channel intersections and undergo further isomerization to yield the above-mentioned products selectively. Similarly, the fraction of *p*-xylene in xylene mixtures can be increased. Figure 5 also shows how acid sites on the surface with large pores and cavities can be effectively blocked by 4-methylquinoline, leaving only the bulk acid sites available to smaller bases that diffuse through the pores.

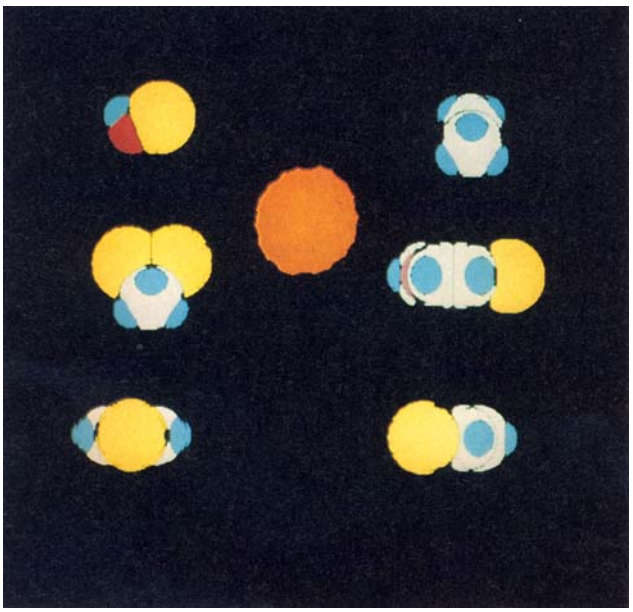

Fig. 4. Illustration of shape selectivity of ZSM-5. The cross section of the straight channel can be compared with the size and shape of the molecules shown (approximately viewed along their molecular axis). Left, from top to bottom: methanol, 2,2-dimethylpentane, *p*-xylene. Right, from top to bottom: *n*-pentane, 4-methylquinoline, *m*-xylene. Yellow: CH_3, white: C, pink: N, red: O, blue: H.

3. Modelling of Defects and Intergrowth Phenomena

3.1. The Zeolites ZSM-5 and ZSM-11

In addition to the illustrative capability that we have described so far, computer simulations can be used to test various structural hypotheses and to check suggested models against the observed results, particularly in the electron microscope. Electron microscopy is probably the most direct technique for identifying intergrowth phenomena in crystalline solids. One recent success has been the identification of the precise nature of the intergrowths involving the closely related zeolites ZSM-5 and ZSM-11[11]. In both ZSM-5 and ZSM-11, chains of five-membered ring building units run parallel to the *c*-axis. The adjacent chains along *a*, however, are related by inversion centers (denoted by i) in ZSM-5 and by mirror planes (denoted by σ) in ZSM-11. Figure 5 illustrates schematically the presence of strips of ZSM-11 in a ZSM-5 matrix. In the computer experiment, various models of ZSM-5/ZSM-11 intergrowths can be constructed by invoking mirror or inversion operations. By placing a "dot" at the locations of the silicon or aluminum atoms, we can create a mask[*] for optical diffraction. The optical diffraction pattern can then be compared with the observed electron diffraction pattern. A typical example characterizing the nature of a particular intergrowth of ZSM-5 and ZSM-11 is shown in Figure 6.

3.2. Twinning in Zeolite Y

Similar studies have been carried out on the twinning across the (111) planes in zeolite Y. If every layer of the (111) planes is twinned with respect to the adjacent layer, the framework, mask, and corresponding optical diffraction pattern in the [111] projection, will be as shown in Figures 7a, b, and c, respectively. The hexagonal symmetry of the pattern is exactly what one would expect[12] for the extended defect structure, which incidentally is identical to that of the zeolite ZSM-3, originally reported by *Kokotailo* and *Ciric*[13]. This can be compared with the results for an untwinned zeolite Y shown in Figure 8. In the [111] projection, even if the twinned layers are juxtaposed between (111) planes, the diffraction pattern and the mask will be

[*] The 'mask' we refer to is the positive film of the structure of an object (Fig. 6a). In an experiment using an optical bench consisting of a laser source, a series of convergent and diffraction lenses, and a recording medium, optical transformation of this mask produces the diffraction pattern shown in Figure 6b. The advantage of such graphical techniques lies in the ability to create large supercells of non-periodic defects of the kind identified here.

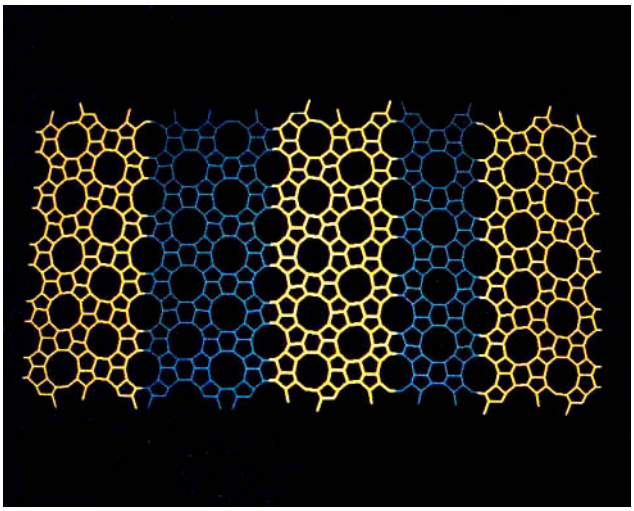

Fig. 5. Schematic view, along the *b*-axis, representing intergrowths between ZSM-5 and ZSM-11 structures. Both these structures are built of five-membered rings forming a chain along the *c*-axis. Adjacent chains, in ZSM-5 (yellow) are related by centers of inversion, whereas those in ZSM-11 (blue) are related by mirror planes, perpendicular to the *a*-axis. The framework remains continuous despite the presence of these defects.

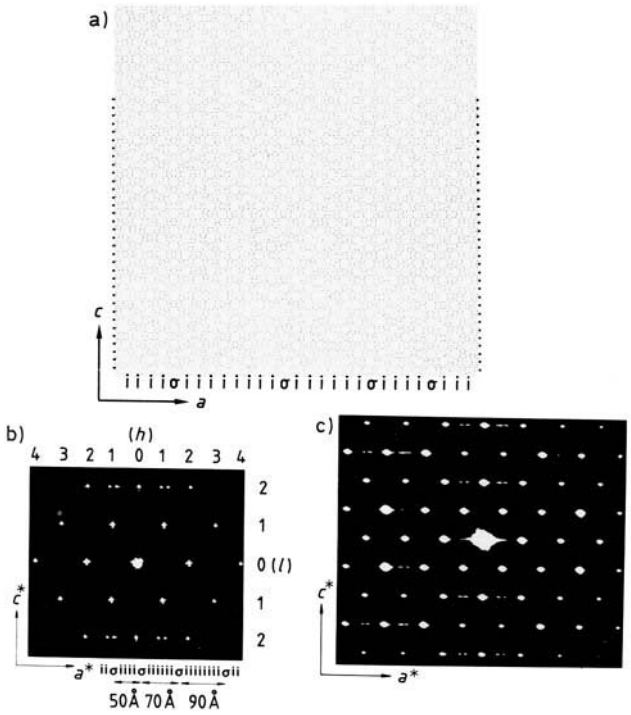

Fig. 6. a) A non-regular model of ZSM-5/ZSM-11 intergrowth of average periodicity $a = 70$ Å (see text). Adjacent strips along a are related by inversion centers i or minor planes σ. The typical minor planes σ in ZSM-11 are separated from each other by various distances (50, 70, 90 Å), which, however, give a, on average. — b) Optical Fourier transform of a) with the reciprocal vectors a^* and c^*, as well as the diffraction orders h and l belonging to the principal reflections of the determined structure ($a_0 = 18.4$ Å). — c) The electron diffraction pattern showing the 66 Å pseudo-periodicity superimposed on the streaks along [100].

the same as those in Figure 8, except for differences in the relative intensities[14]. However, viewing along [110] one can identify the defect regions of the crystal. For a hypothetical case in which every third layer is a twin of the second layer of the (111) planes, the optical mask is shown in

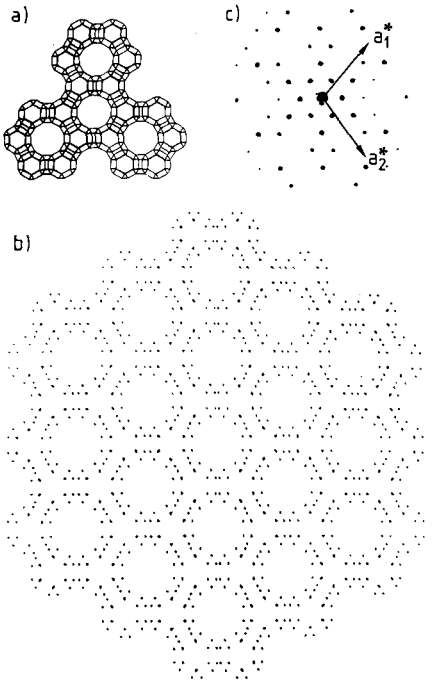

Fig. 7. a) Framework of the recurrently twinned faujasite. Here twinning occurs at every adjacent (111) plane in the faujasite structure. The resulting structure is hexagonal and the plane of projection now becomes $(001)_{hex}$. b) The mask representing the framework is the same projection but depicting the location of Si (or Al) atoms, without the bonds. c) The optical transform of b), the zone axis being $[001]_{hex}$.

color (Fig. 9) to distinguish the twinned layers. If the twinning had been random, the optical diffraction pattern of the corresponding model would show streaking along [111].

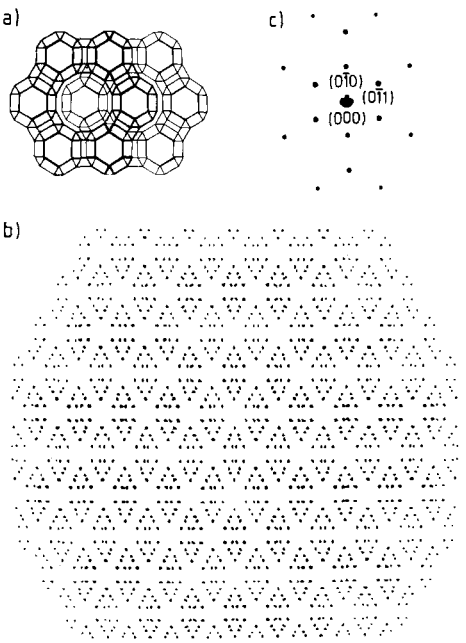

Fig. 8. a) Framework of the faujasite structure in the [111] projection; b) a "mask" depicting the locations of the Si (or Al) atoms; c) the corresponding optical transform of b).

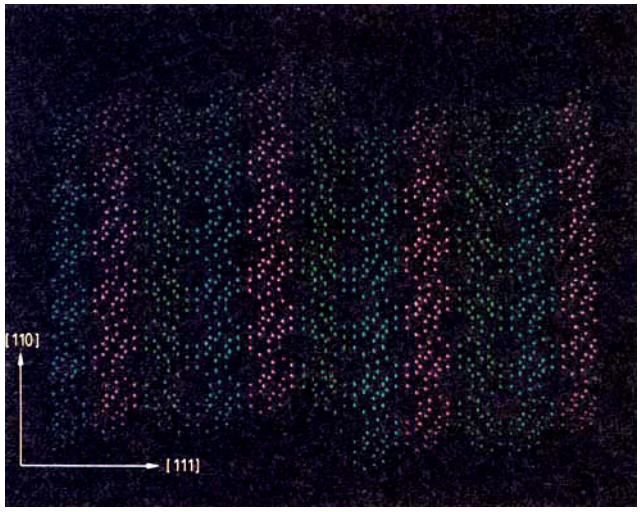

Fig. 9. A hypothetical model of faujasite, viewed along [110], in which twinning occurs at every third layer of (111) planes (blue-red-green) running parallel to the vertical axis in the figure.

3.3. Variations in Stacking Sequences

There is a whole family of related zeolitic structures of similar chemical composition with six-membered rings of SiO_4 tetrahedra that are stacked in three different ways (A, B, and C, see Fig. 10) along the hexagonal *c*-axis, giving rise to an almost infinite number of framework structures[15]. Although, by convention, these structures can be classified as polytypes, their steric arrangements actually differ. If only two types of sequences are present in a structure in any order, they will have large open channels in the *c* direction, as in offretite (see Fig. 10 (top)). On the other hand, if all three stacking arrangements are present, there will be long and short cages, (with 12-membered ring apertures effectively blocked, as shown in Figure 10 (middle)) depending on the precise sequence present; e.g. liottite and afghanite. In Table 1 we list some of the known zeolites possessing stacking variations of this kind. Stacking faults in the parent structures have often been noticed, particularly in high resolution lattice images[16] in the electron microscope. Depending on the stacking sequence present, the relative positions of the 8-membered ring apertures in the [110] zone differ and are easily seen in the image, provided the material is electron-beam stable and the zone axis is accessible.

Table 1. Chabazite family of zeolites with their stacking properties.

Name	Abbr.	Space group	Lattice parameters [Å] *a*	*c*	Stacking sequence
Afghanite	AFG	$P6_3/mmc$	12.8	21.4	ABABACAC
Cancrinite	CAN	$P6_3/mmc$	12.8	5.1	AB
Chabazite	CHA	$R\bar{3}m$	13.2	15.1	AABBCC
TMA-E(AB)	EAB	$P6_3/mmc$	13.3	15.2	ABBACC
Erionite	ERI	$P6_3/mmc$	13.3	15.1	AABAAC
Gmelinite	GME	$P6_3/mmc$	13.8	10.0	AABB
Levyne	LEV	$R\bar{3}m$	13.3	23.0	AABCCABBC
Liottite	LIO	$P\bar{6}m2$	12.8	16.1	ABABAC
Losode	LOS	$P6_3/mmc$	12.9	10.5	ABAC
Offretite	OFF	$P\bar{6}m2$	13.3	7.6	AAB
Sodalite	SOD	$I\bar{4}3m$	8.9	—	ABC

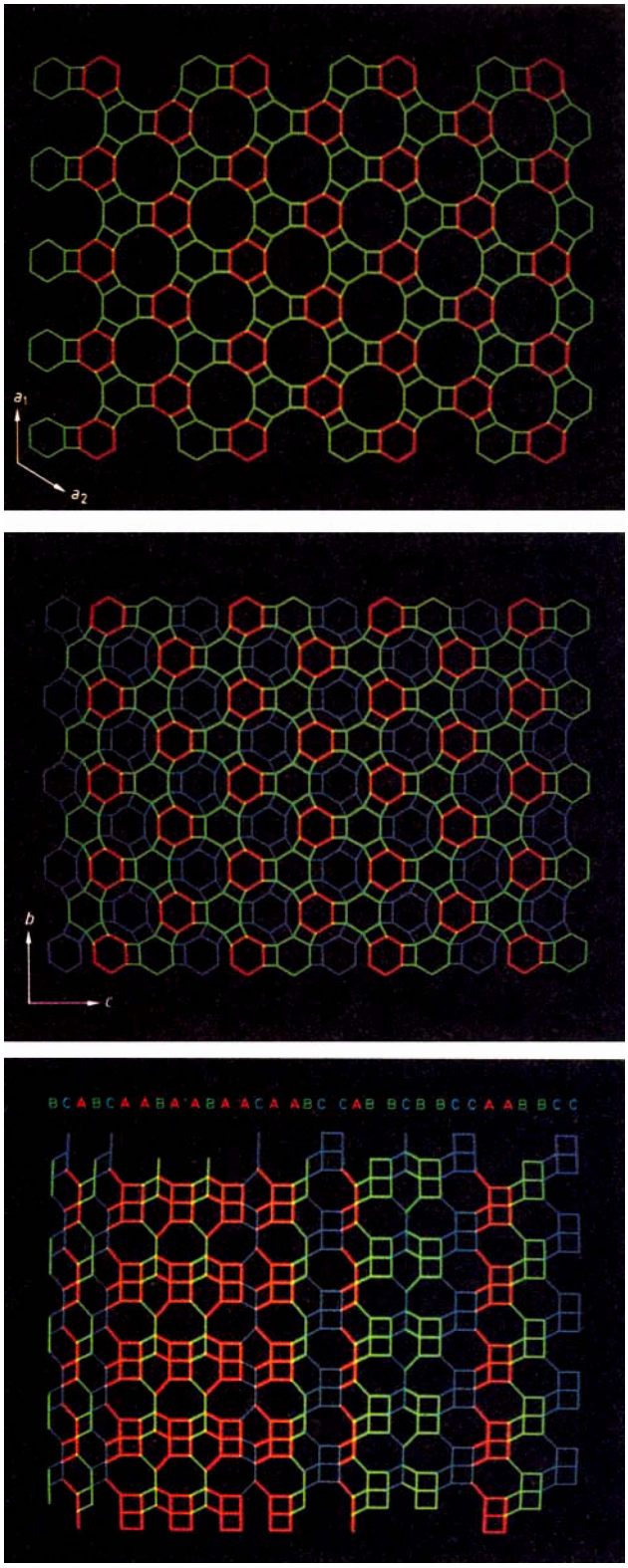

Fig. 10. Schematic representation of the "chabazite" family of zeolites: top: "AB" and middle: "ABC" stacking sequences viewed along the hexagonal axis; bottom: The possibility of intergrowths and stacking faults among these zeolites is shown schematically, viewed on the *bc* plane.

We have devised a novel method[17] of simulating any desired stacking sequence, from which we make a direct comparison with the lattice image. In this way, one may identify even an isolated stacking fault in such materials. Figure 10 (bottom) describes schematically the principle

behind such computer experiments. It clearly demonstrates how various zeolites, differing in their ordered sequences, can intergrow with each other. We would particularly like to draw attention to the relative arrangements of the eight-membered ring apertures resulting from such intergrowths, which, with continuing improvements in technique, will become identifiable in the high resolution image[17].

3.4. Simulation of Non-Coherent Interfaces between Crystallites

There is increasing experimental evidence to suggest growths of two different, yet related frameworks of zeolitic structures upon one another. One such piece of evidence was uncovered by *Kerr* et al.[18] in the case of zeolite L and offretite (or erionite) growing across a common interface. Similar occurrences in the cases of synthetic mazzite and offretite, and mazzite and zeolite Y have also been observed[19]. Simulation of such interfaces requires large periodicities in the growth plane, sometimes in excess of 100 Å. Manipulation of such large unit cells in a graphics system is probably a convenient way of visualizing the structural consequences of such phenomena. We give below one specific example, namely the presence of the $\sqrt{13}\sqrt{13}$ R32.2° coincident lattice in the growth of zeolite L (see Fig. 11). Similar descriptions apply to the systems mentioned above[20].

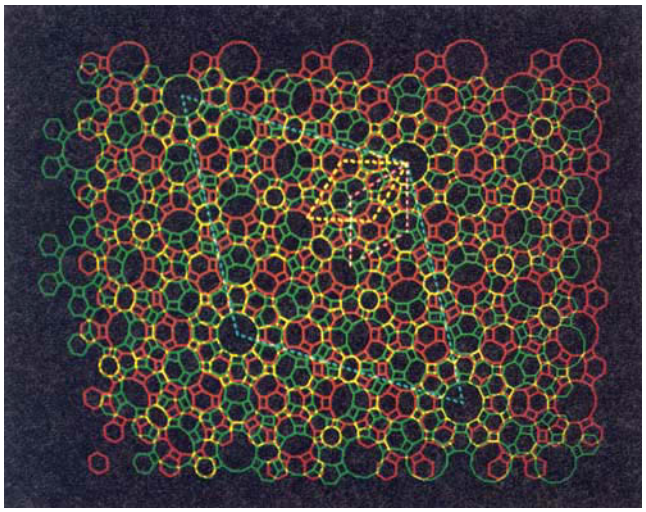

Fig. 11. Plan view (down [001]) of the coincidence boundary ($\sqrt{13}\sqrt{13}$ R32.2°) generated by rotating one half of the crystal of zeolite "L" about [001] by 32.2° with respect to the other (each vertex denotes a Si or Al site joined together via oxygens, not shown here). The repeat distances in the coincident lattice exceeds the original hexagonal mesh ($a_0 = 18.4$ Å) by $\sqrt{13}$.

In the high resolution lattice image of zeolite L in the [001] zone, small domains of lattice periodicity $a_0\sqrt{13}$ ($a_0 = 18.4$ Å) were frequently observed. Optical diffractograms of the image indicated a near 30° rotation of one half of the crystal over another. Exact coincidence of the lattice at the interface, however, occurs at 32.2°. A schematic diagram of such a coincidence boundary and its consequence, the overlap of fewer open tunnels, is shown in Figure 11. One may note that even though there is a coincidence of lattice there is no coincidence of atomic positions. Figure 11 clearly shows that following the introduction of one such boundary there is a reduction in the number of open channels per unit area (only 8 percent in zeolite L) with a concomitant reduction in the diffusivity of molecules along [001] channels.

4. Interaction Energies of Organic Molecules and Zeolites

The sorption and diffusion of an organic molecule within the zeolite is primarily governed by the shape and size of the cages and channels in the framework, and we have seen the capability of computer graphics in illustrating these aspects. In this section, we describe how an organic molecule can be "guided" through the cavities and how one can estimate, quantitatively, the energetics involved in such a process. This work is ideally carried out interactively using a graphics terminal; the movement of the molecule within the framework and the interaction energies associated with the locations and orientation of the molecule can be monitored in real time.

In order to calculate the interaction energies, we require a model that is both reasonably accurate and, for interactive computations, uses relatively fast algorithms. For simplicity we ignore the interactions between the organic molecules themselves, i.e. we consider an infinitely dilute system. Similarly we assume that the framework remains unaltered by the introduction of the guest molecules. (There are good physico-chemical reasons for supposing that some organic molecules will perturb the zeolitic framework structure. The nature of this perturbation could itself be monitored by computer graphical methods of the kind described in this article.)

The model used in this work is a simple empirical treatment of van der Waals energy, with the addition of an electrostatic term. The expression used for non-bonded atom pairs is

$$U(r) = \frac{A\exp(-Br)}{r^D} - \frac{C}{r^6} + \frac{Kq_1q_2}{r}$$

where A, B, C and D are constants, q_1 and q_2 are the atomic charges, K is a unit conversion constant, and r is the distance between the atom pair.

The parameterization of the van der Waals part of this equation is that due to *Del Re* et al.[21], using the coefficients of *Kiselev* et al.[22]. Most of the organic molecules of interest are electrically neutral, but the net charges on the atoms can be calculated using molecular orbital methods[23]. Similarly, theoretical estimates[24] of the charges on the framework atoms are necessary in order to describe the electrostatic interactions, which are relatively long range. The value of the permittivity can be included in the constant K, and in this work a value of unity was used.

The total interaction energy is derived from the sum of the atom-atom terms, an assumption widely and successfully used in predicting the conformations of proteins and the packing of molecules in the solid state. A further ap-

proximation has been made to speed up the calculation for widely separated atoms: the short-range repulsive terms are ignored, and the attractive and electrostatic terms are estimated for groups of atoms, rather than for individual atoms[25].

We illustrate the application of the above procedure by describing results on the adsorption of benzene in silicalite, an aluminum-free zeolite that is isostructural with ZSM-5. We have chosen this system not only because of its industrial importance, but also for simplicity, since the calculations are not hampered by uncertainties in the locations of aluminum atoms and extra-framework cations. The benzene molecule is placed at a suitable starting position within the straight channel of a fragment of zeolite containing about 3500 atoms (Fig. 12). The interaction energy between the benzene molecule and the silicate framework is then calculated at intervals of 0.4 Å along the channel for a range of angular orientations of the molecule about the two-fold axis of the channel.

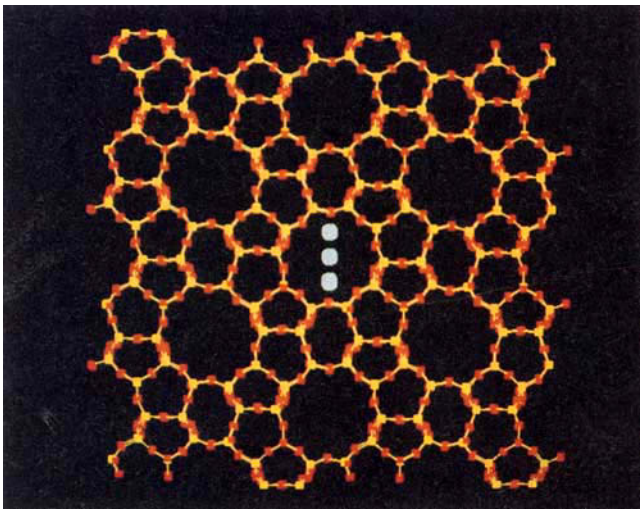

Fig. 12. A molecule of benzene in the straight channel of ZSM-5. For the energy calculations, the orientation of the molecule is varied such that the long molecular axis remains always parallel to the channel axis b. It is the angle θ between the short molecular axis and the maximum diameter (in projection) of the channel that is changed at regular intervals; in this case $\theta = 0°$.

In a typical calculation, over 1600 values of the interaction energy are stored with the corresponding position and orientation of the molecule. Figure 13 shows the energy at a fixed angular orientation as a function of the distance along the straight channel. A more effective method of displaying these results is in the form of a contour map using colored regions to represent different energy levels in areas of the conformational space over which the calculation was performed. The maps reproduce geometrical features such as the symmetry of the system, and they also reveal the restrictions on the movement of the molecule within the channel. For example, from Figure 14 one readily sees that facile molecular diffusion along the channel occurs only for a limited range of angular orientations. The colored contours also show the energy barriers and the greater conformational freedom encountered at the intersections where the straight and sinusoidal channels meet.

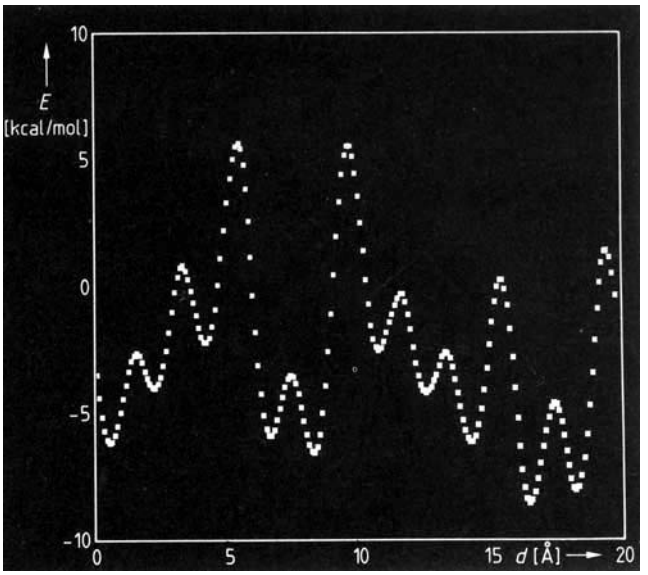

Fig. 13. A plot of interaction energy E against distance of travel (from an arbitrary origin through the entire unit cell length of 20 Å) for a benzene molecule moving along the straight channel direction, b, in silicalite, the pure silica variety of ZSM-5 (cf. Fig. 12), at a fixed orientation, i.e. $\theta = 30°$.

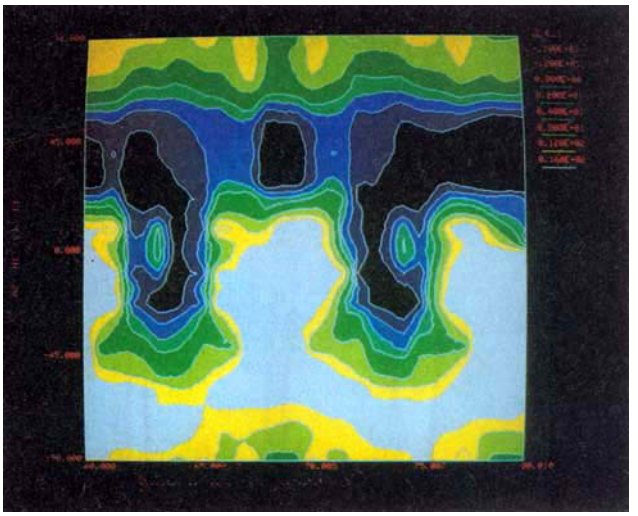

Fig. 14. Adsorption energy contours based on the results of plots like Figure 13 for all possible orientations of θ graded from positive to negative values in terms of color codes (black -10, dark blue -2, marine blue 0, light-green 2, dark green 4, yellow-green 8, yellow 12, light blue 16 kcal/mol) are plotted as a function of θ (ordinate) and the distance (Å) along the b channel. The abscissa values (from left to right) are 60, 65, 70, 75, and 80 Å; the ordinate values (from bottom to top), -90, -45, 0, 45, and 90°.

One of the great merits of using interactive graphics procedures is the ability to freeze these optimum configurations to allow for more detailed studies, including the influence of refined potentials and larger segments of the framework. We expect that this approach will play an important role in future studies on adsorption and diffusion processes in zeolites.

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On Stars, Their Evolution and Their Stability (Nobel Lecture)**

By Subrahmanyan Chandrasekhar*

1. Introduction

When we think of atoms, we have a clear picture in our minds: a central nucleus and a swarm of electrons surrounding it. We conceive them as small objects of sizes measured in Ångstroms ($\sim 10^{-8}$ cm); and we know that some hundred different species of them exist. This picture is, of course, quantified and made precise in modern quantum theory. And the success of the entire theory may be traced to two basic facts: *first*, the Bohr radius of the ground state of the hydrogen atom, namely

$$\frac{h^2}{4\pi^2 m e^2} \sim 0.5 \times 10^{-8}\ \text{cm} \qquad (1)$$

where h is Planck's constant, m is the mass of the electron, and e is its charge, provides a correct measure of atomic dimensions; and *second*, the reciprocal of *Sommerfeld's fine-structure constant*,

$$\frac{hc}{2\pi e^2} \sim 137 \qquad (2)$$

gives the maximum positive charge of the central nucleus that will allow a stable electron-orbit around it. This maximum charge for the central nucleus arises from the effects of special relativity on the motions of the orbiting electrons.

We now ask: can we understand the basic facts concerning stars as simply as we understand atoms in terms of the two combinations of natural constants (1) and (2)? In this lecture, I shall attempt to show that in a limited sense we can.

The most important fact concerning a star is its mass. It is measured in units of the mass of the sun, $\odot$, which is 2×10^{33} g; stars with masses very much less than, or very much more than, the mass of the sun are relatively infrequent. The current theories of stellar structure and stellar evolution derive their successes largely from the fact that the following combination of the dimensions of a mass provides a correct measure of stellar masses:

$$\left(\frac{hc}{G}\right)^{3/2} \frac{1}{H^2} \simeq 29.2\ \odot \qquad (3)$$

where G is the constant of gravitation and H is the mass of the hydrogen atom. In the first half of the lecture, I shall essentially be concerned with the question: how does this come about?

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2. The Role of Radiation Pressure

A central fact concerning normal stars is the role which radiation pressure plays as a factor in their hydrostatic equilibrium, Precisely, the equation governing the hydrostatic equilibrium of a star is

$$\frac{dP}{dr} = -\frac{GM(r)}{r^2}\rho \tag{4}$$

where P denotes the total pressure, ρ the density, and $M(r)$ is the mass interior to a sphere of radius r. There are two contributions to the total pressure P: that due to the material and that due to the radiation. On the assumption that the matter is in the state of a perfect gas in the classical Maxwellian sense, the material or the gas pressure is given by

$$p_{\text{gas}} = \frac{k}{\mu H}\rho T \tag{5}$$

where T is the absolute temperature, k is the Boltzmann constant, and μ is the mean molecular weight (which under normal stellar conditions is ≈ 1.0). The pressure due to radiation is given by

$$p_{\text{rad}} = \frac{1}{3}aT^4 \tag{6}$$

where a denotes Stefan's radiation-constant. Consequently, if radiation contributes a fraction $(1-\beta)$ to the total pressure, we may write

$$P = \frac{1}{3}\frac{1}{1-\beta}aT^4 = \frac{1}{\beta}\frac{k}{\mu H}\rho T \tag{7}$$

To bring out explicitly the role of the radiation pressure in the equilibrium of a star, we may eliminate the temperature, T, from the foregoing equations and express P in terms of ρ and β, instead of in terms of ρ and T. We find

$$T = \left(\frac{k}{\mu H}\frac{3}{a}\frac{1-\beta}{\beta}\right)^{1/3}\rho^{1/3} \tag{8}$$

and

$$P = \left[\left(\frac{k}{\mu H}\right)^4\frac{3}{a}\frac{1-\beta}{\beta^4}\right]^{1/3}\rho^{4/3} = C(\beta)\rho^{4/3} \text{ (say)} \tag{9}$$

The importance of this ratio, $(1-\beta)$, for the theory of stellar structure was first emphasized by *Eddington*. Indeed, he related it, in a famous passage in his book on *The Internal Constitution of the Stars*, to the "happening of the stars"[1]. A more rational version of *Eddington*'s argument which, at the same time, isolates the combination (3) of the natural constants is the following:

There is a general theorem[2] which states that the pressure, P_c, at the centre of a star of a mass M in hydrostatic equilibrium in which the density, $\rho(r)$, at a point at a radial distance, r, from the centre does not exceed the mean density, $\bar{\rho}(r)$, interior to the same point r, must satisfy the inequality

$$\tfrac{1}{2}G(\tfrac{4}{3}\pi)^{1/3}\bar{\rho}^{4/3}M^{2/3} \le P_c \le \tfrac{1}{2}G(\tfrac{4}{3}\pi)^{1/3}\rho_c^{4/3}M^{2/3} \tag{10}$$

where $\bar{\rho}$ denotes the mean density of the star and ρ_c its density at the centre. The content of the theorem is no more than the assertion that the actual pressure at the centre of a star must be intermediate between those at the centres of the two configurations of uniform density, one at a density equal to the mean density of the star, and the other at a density equal to the density ρ_c at the centre (see Fig. 1). If the inequality (10) should be violated then there must, in general, be some regions in which adverse density gradients must prevail; and this implies instability. In other words, we may consider conformity with the inequality (10) as equivalent to the condition for the stable existence of stars.

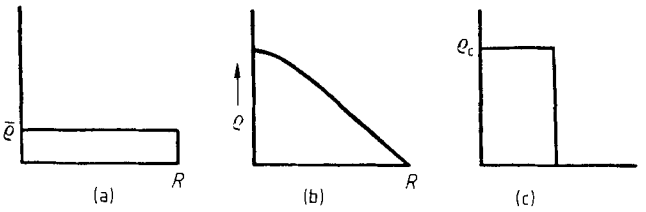

Fig. 1. A comparison of an inhomogeneous distribution of density in a star (b) with the two homogeneous configurations with the constant density equal to the mean density (a) and equal to the density at the centre (c).

The right-hand side of the inequality (10) together with P given by equation (9), yields, for the stable existence of stars, the condition

$$\left[\left(\frac{k}{\mu H}\right)^4\frac{3}{a}\frac{1-\beta_c}{\beta_c^4}\right]^{1/3} \le \left(\frac{\pi}{6}\right)^{1/3}GM^{2/3} \tag{11}$$

or, equivalently

$$M \ge \left(\frac{6}{\pi}\right)^{1/2}\left[\left(\frac{k}{\mu H}\right)^4\frac{3}{a}\frac{1-\beta_c}{\beta_c^4}\right]^{1/2}\frac{1}{G^{3/2}} \tag{12}$$

where in the foregoing inequalities, β_c is a value of β at the centre of the star. Now Stefan's constant, a, by virtue of Planck's law, has the value

$$a = \frac{8\pi^5k^4}{15h^3c^3} \tag{13}$$

Inserting this value a in the equality (12), we obtain

$$\mu^2M\left(\frac{\beta_c^4}{1-\beta_c}\right)^{1/2} \ge \frac{(135)^{1/2}}{2\pi^3}\left(\frac{hc}{G}\right)^{3/2}\frac{1}{H^2} = 0.1873\left(\frac{hc}{G}\right)^{3/2}\frac{1}{H^2} \tag{14}$$

We observe that the inequality (14) has isolated the combination (3) of natural constants of the dimensions of a mass; by inserting its numerical value given in equation (3), we obtain the inequality

$$\mu^2M\left(\frac{\beta_c^4}{1-\beta_c}\right)^{1/2} \ge 5.48\,\odot \tag{15}$$

This inequality provides an upper limit to $(1-\beta_c)$ for a star of a given mass. Thus,

$$1-\beta_c \leq 1-\beta_* \tag{16}$$

where $(1-\beta_*)$ is uniquely determined by the mass M of the star and the mean molecular weight, μ, by the quartic equation (17):

$$\mu^2 M = 5.48 \left(\frac{1-\beta_*}{\beta_*^4}\right)^{1/2} \odot \tag{17}$$

In Table 1, we list the values of $1-\beta_*$ for several values of $\mu_2 M$. From this table it follows in particular, that for a star of solar mass with a mean molecular weight equal to 1, the radiation pressure at the centre cannot exceed 3 percent of the total pressure.

Table 1. The maximum radiation pressure, $(1-\beta_*)$, at the centre of a star of a given mass, M.

$1-\beta_*$	$M\mu^2/\odot$	$1-\beta_*$	$M\mu^2/\odot$
0.01	0.56	0.50	15.49
0.03	1.01	0.60	26.52
0.10	2.14	0.70	50.92
0.20	3.83	0.80	122.5
0.30	6.12	0.85	224.4
0.40	9.62	0.90	519.6

What do we conclude from the foregoing calculation? We conclude that to the extent equation (17) is at the base of the equilibrium of actual stars, to that extent the combination of natural constants (3), providing a mass of proper magnitude for the measurement of stellar masses, is at the base of a physical theory of stellar structure.

3. Do Stars have Enough Energy to Cool?

The same combination of natural constants (3) emerged soon afterwards in a much more fundamental context of resolving a paradox *Eddington* had formulated in the form of an aphorism: "a star will need energy to cool". The paradox arose while considering the ultimate fate of a gaseous star in the light of the then new knowledge that white-dwarf stars, such as the companion of Sirius, exist which have mean densities in the range 10^5-10^7 g cm^{-3}. As *Eddington* stated[3]:

> I do not see how a star which has once got into this compressed state is ever going to get out of it. ... It would seem that the star will be in an awkward predicament when its supply of subatomic energy fails.

The paradox posed by *Eddington* was reformulated in clearer physical terms by *R. H. Fowler*[4]. His formulation was the following:

> The stellar material, in the white-dwarf state, will have radiated so much energy that it has less energy than the same matter in normal atoms expanded at the absolute zero of temperature. If part of it were removed from the star and the pressure taken off, what could it do?

Quantitatively, *Fowler*'s question arises in this way:

An estimate of the electrostatic energy, E_V, per unit volume of an assembly of atoms, of atomic number Z, ionized down to bare nuclei, is given by

$$E_V = 1.32 \times 10^{11} Z^2 \rho^{4/3} \tag{18}$$

while the kinetic energy of thermal motions, E_{kin}, per unit volume of free particles in the form of a perfect gas of density, ρ, and temperature, T, is given by

$$E_{kin} = \frac{3}{2}\frac{k}{\mu H}\rho T = \frac{1.24 \times 10^8}{\mu}\rho T \tag{19}$$

Now if such matter were released of the pressure to which it is subject, it can resume a state of ordinary normal atoms only if

$$E_{kin} > E_V \tag{20}$$

or, according to equations (18) and (19), only if

$$\rho < \left(0.94 \times 10^{-3} \frac{T}{\mu Z^2}\right)^3 \tag{21}$$

This inequality will be clearly violated if the density is sufficiently high. This is the essence of *Eddington*'s paradox as formulated by *Fowler*. And *Fowler* resolved this paradox in 1926 in a paper[4] entitled "Dense Matter"—one of the great landmark papers in the realm of stellar structure: in it, the notions of Fermi statistics and of electron degeneracy are introduced for the first time.

4. *Fowler*'s Resolution of Eddington's Paradox; the Degeneracy of the Electrons in White-Dwarf Stars

In a completely degenerate electron gas, all the available parts of the phase space with momenta less than a certain "threshold" value p_0—the Fermi threshold—are occupied consistently with the Pauli exclusion-principle, i.e., with two electrons per "cell" of volume h^3 of the six-dimensional phase space. Therefore, if $n(p)\,dp$ denotes the number of electrons per unit volume between p and $p+dp$, then the assumption of complete degeneracy is equivalent to the assertion

$$\begin{aligned} n(p) &= \frac{8\pi}{h^3}p^2 \quad (p \leq p_0) \\ &= 0 \qquad (p > p_0) \end{aligned} \tag{22}$$

The value of the threshold momentum, p_0, is determined by the normalization condition

$$n = \int_0^{p_0} n(p)\,dp = \frac{8\pi}{3h^3}p_0^3 \tag{23}$$

where n denotes the total number of electrons per unit volume.

For the distribution given by (22), the pressure p and the kinetic energy E_{kin} of the electrons (per unit volume) are given by

$$P=\frac{8\pi}{3h^3}\int_0^{p_0} p^3 v_p \, dp \tag{24}$$

and

$$E_{kin}=\frac{8\pi}{h^3}\int_0^{p_0} p^2 T_p \, dp, \tag{25}$$

where v_p and T_p are the velocity and the kinetic energy of an electron having momentum p, respectively.

If we set

$$v_p=p/m \quad \text{and} \quad T_p=p^2/2m, \tag{26}$$

appropriate for non-relativistic mechanics, in equations (24) and (25), we find

$$P=\frac{8\pi}{15h^3m}p_0^5=\frac{1}{20}\left(\frac{3}{\pi}\right)^{2/3}\frac{h^2}{m}n^{5/3} \tag{27}$$

and

$$E_{kin}=\frac{8\pi}{10h^3m}p_0^5=\frac{3}{40}\left(\frac{3}{\pi}\right)^{2/3}\frac{h^2}{m}n^{5/3} \tag{28}$$

Fowler's resolution of *Eddington*'s paradox consists in this: at the temperatures and densities that may be expected to prevail in the interiors of the white-dwarf stars, the electron will be highly degenerate and E_{kin} must be evaluated in accordance with equation (28) and *not* in accordance with equation (19); and equation (28) gives

$$E_{kin}=1.39\times 10^{13}(\rho/\mu)^{5/3} \tag{29}$$

Comparing now the two estimates (18) and (29), we see that for matter of the density occurring in the white dwarfs, namely $\rho\approx 10^5$ g cm^{-3}, the total kinetic energy is about two to four times the negative potential-energy; and *Eddington*'s paradox does not arise. *Fowler* concluded his paper with the following highly perceptive statement:

> The black-dwarf material is best likened to a single gigantic molecule in its lowest quantum state. On the Fermi-Dirac statistics, its high density can be achieved in one and only one way, in virtue of a correspondingly great energy content. But this energy can no more be expended in radiation than the energy of a normal atom or molecule. The only difference between black-dwarf matter and a normal molecule is that the molecule can exist in a free state while the black-dwarf matter can only so exist under very high external pressure.

5. The Theory of the White-Dwarf Stars; the Limiting Mass

The internal energy $(3P/2)$ of a degenerate electron gas that is associated with a pressure P is *zero-point energy*; and the essential content of *Fowler*'s paper is that this zero-point energy is so great that we may expect a star to eventually settle down to a state in which all of its energy is of this kind. *Fowler*'s argument can be more explicitly formulated in the following manner[5].

According to the expression for the pressure given by equation (27), we have the relation

$$P=K_1\rho^{5/3} \quad \text{where} \quad K_1=\frac{1}{20}\left(\frac{3}{\pi}\right)^{2/3}\frac{h^2}{m(\mu_e H)^{5/3}} \tag{30}$$

where μ_e is the mean molecular weight per electron. An equilibrium configuration in which the pressure, P, and the density, ρ, are related in the manner

$$P=K\rho^{1+1/n} \tag{31}$$

is an *Emden polytrope* of index n. The degenerate configurations built on the equation of state (30) are therefore polytropes of index 3/2; and the theory of polytropes immediately provides the relation

$$K_1=0.4242\,(GM^{1/3}R) \tag{32}$$

or, numerically, for K_1 given by equation (30)

$$\log_{10}(R/R_\odot)=-\tfrac{1}{3}\log_{10}(M/\odot)-\tfrac{5}{3}\log_{10}\mu_e-1.397 \tag{33}$$

For a mass equal to the solar mass and $\mu_e=2$, the relation (33) predicts $R=1.26\times 10^{-2}R_\odot$ and a mean density of 7.0×10^5 gm/cm^3. These values are precisely of the order of the radii and mean densities encountered in white-dwarf stars. Moreover, according to equations (32) and (33), the radius of the white-dwarf configuration is inversely proportional to the cube-root of the mass. On this account, finite equilibrium configurations are predicted for all masses. And it came to be accepted that the white-dwarfs represent the last stages in the evolution of all stars.

But it soon became clear that the foregoing simple theory based on *Fowler*'s premises required modifications. For, the electrons at their threshold energies at the centres of the degenerate stars begin to have velocities comparable to that of light as the mass increases. Thus, already for a degenerate star of solar mass (with $\mu_e=2$) the central density ρ_c (which is about six times the mean density) is 4.19×10^6 g/cm^3; and this density corresponds to a threshold momentum $p_0=1.29\,mc$ and a velocity which is $0.63c$. Consequently, the equation of state must be modified to take into account the effects of special relativity. And this is easily done by inserting in equations (24) and (25) the relations

$$v_p=\frac{p}{m(1+p^2/m^2c^2)^{1/2}} \quad \text{and} \quad T_p=mc^2[(1+p^2/m^2c^2)^{1/2}-1] \tag{34}$$

in place of the non-relativistic relations (26). We find that the resulting equation of state can be expressed parametrically in the form

$$P=Af(x) \quad \text{and} \quad \rho=Bx^3 \tag{35}$$

where

$$A = \frac{\pi m^4 c^5}{3h^3}, \quad B = \frac{8\pi m^3 c^3 \mu_e H}{3h^3} \tag{36}$$

and

$$f(x) = x(x^2+1)^{1/2}(2x^2-3) + 3\sinh^{-1} x \tag{37}$$

And similarly

$$E_{kin} = A\,g(x) \tag{38}$$

where

$$g(x) = 8x^3[(x^2+1)^{1/2} - 1] - f(x) \tag{39}$$

According to equations (35) and (36), the pressure approximates the relation (30) for low enough electron concentrations ($x \ll 1$); but for increasing electron concentrations ($x \gg 1$), the pressure tends to[6]

$$P = \frac{1}{8}\left(\frac{3}{\pi}\right)^{1/3} hc\, n^{4/3} \tag{40}$$

This limiting form of relation can be obtained very simply by setting $v_p = c$ in equation (24); then

$$P = \frac{8\pi c}{3h^3}\int_0^{p_0} p^3\,dp = \frac{2\pi c}{3h^3}p_0^4 \tag{41}$$

and the elimination of p_0 with aid of equation (23) directly leads to equation (40).

While the modification of the equation of state required by the special theory of relativity appears harmless enough, it has, as we shall presently show, a dramatic effect on the predicted mass-radius relation for degenerate configurations.

The relation between P and ρ corresponding to the limiting form (41) is

$$P = K_2\rho^{4/3} \quad \text{where} \quad K_2 = \frac{1}{8}\left(\frac{3}{\pi}\right)^{1/3}\frac{hc}{(\mu_e H)^{4/3}} \tag{42}$$

In this limit, the configuration is an Emden polytrope of index 3. And it is well known that when the polytropic index is 3, the mass of the resulting equilibrium configuration is uniquely determined by the constant of proportionality, K_2, in the pressure-density relation. We have accordingly

$$\begin{aligned} M_{limit} &= 4\pi\left(\frac{K_2}{\pi G}\right)^{3/2}(2.018) \\ &= 0.197\left(\frac{hc}{G}\right)^{3/2}\frac{1}{(\mu_e H)^2} = 5.76\mu_e^{-2}\odot \end{aligned} \tag{43}$$

(In equation (43), 2.018 is a numerical constant derived from the explicit solution of the Lane-Emden equation for $n = 3$.)

It is clear from general considerations[7] that *the exact mass-radius relation for the degenerate configurations must provide an upper limit to the mass of such configurations given by equation* (43); *and further, that the mean density of the configuration must tend to infinity,* while the radius tends to zero, and $M \to M_{limit}$. These conditions, straightforward as they are, can be established directly by considering the equilibrium of configurations built on the exact equation of state given by equations (35)—(37). It is found that the equation governing the equilibrium of such configurations can be reduced to the form[8,9]

$$\frac{1}{\eta^2}\frac{d}{d\eta}\left(\eta^2\frac{d\phi}{d\eta}\right) = -\left(\phi^2 - \frac{1}{y_0^2}\right)^{3/2} \tag{44}$$

where

$$y_0^2 = x_0^2 + 1 \tag{45}$$

mcx_0 denotes the threshold momentum of the electrons at the centre of the configuration, and η measures the radial distance in the unit

$$\left(\frac{2A}{\pi G}\right)^{1/2}\frac{1}{By_0} = l_1 y_0^{-1} \tag{46}$$

By integrating equation (44), with suitable boundary conditions and for various initially prescribed values of y_0, we can derive the exact mass-radius relation, as well as the other equilibrium properties, of the degenerate configurations. The principal results of such calculations are illustrated in Figures 2 and 3.

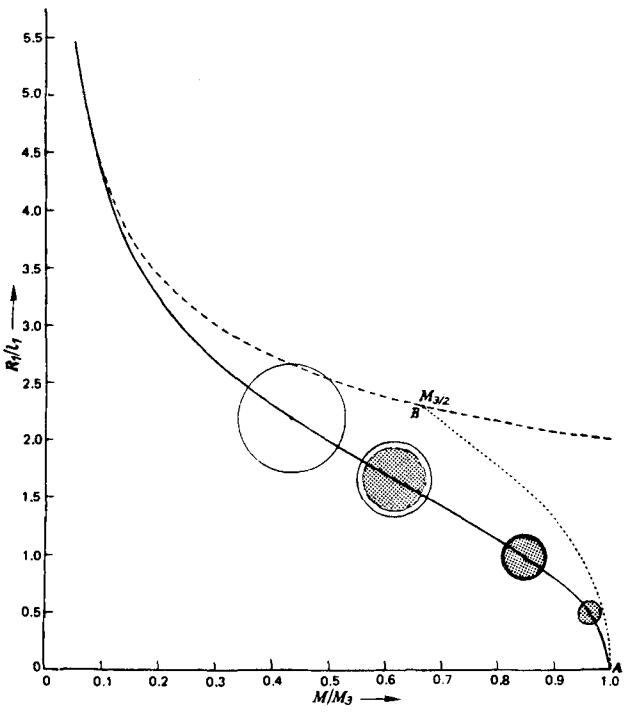

Fig. 2. The full-line curve represents the exact (mass-radius)-relation (l_1 is defined in equation (46) and M_3 denotes the limiting mass). This curve tends asymptotically to the ---- curve appropriate to the low-mass degenerate configurations, approximated by polytropes of index 3/2. The regions of the configurations which may be considered as relativistic [$\rho > (K_1/K_2)^3$] are shown shaded (from [9]).

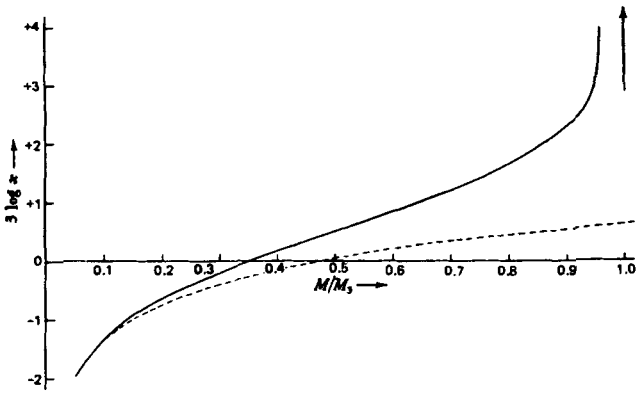

Fig. 3. The full-line curve represents the exact (mass-density)-relation for the highly collapsed configurations. This curve tends asymptotically to the dotted curve as $M \to 0$ (from [9]).

The important conclusions which follow from the foregoing considerations are: *first,* there is an upper limit, M_{limit}, to the mass of stars which can become degenerate configurations, as the last stage in their evolution; and *second,* that stars with $M > M_{\text{limit}}$ must have end states which cannot be predicted from the considerations we have presented so far. And finally, we observe that the combination of the natural constant (3) now emerges in the fundamental context of M_{limit} given by equation (43): its significance for the theory of stellar structure and stellar evolution can no longer be doubted.

6. Under What Conditions Can Normal Stars Develop Degenerate Cores?

Once the upper limit to the mass of completely degenerate configurations had been established, the question required to be resolved was how to relate its existence to the evolution of stars from their gaseous state. If a star has a mass less than M_{limit}, the assumption that it will eventually evolve towards the completely degenerate state appears reasonable. But what if its mass is greater than M_{limit}? Clues as to what might ensue were sought in terms of the equations and inequalities of Sections 2 and 3[10,11].

The first question that had to be resolved concerns the circumstances under which a star, initially gaseous, will develop degenerate cores. From the physical side, the question, when departures from the perfect-gas equation of state (5) will set in and the effects of electron degeneracy will be manifested, can be readily answered.

Suppose, for example, that we continually and steadily increase the density, at constant temperature, of an assembly of free electrons and atomic nuclei in a highly ionized state and initially in the form of a perfect gas governed by the equation of state (5). At first the electron pressure will increase linearly with ρ; but soon departures will set in and eventually the density will increase in accordance with the equation of state that describes the fully degenerate electron-gas (see Fig. 4). The remarkable fact is that this limiting form of the equation of state is independent of temperature.

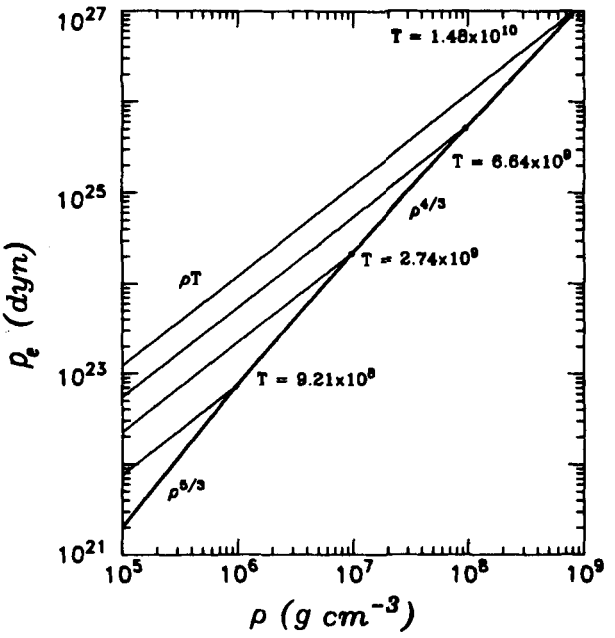

Fig. 4. Illustrating how by increasing the density at constant temperature degeneracy always sets in.

However, to examine the circumstances when, during the course of evolution, a star will develop degenerate cores, it is more convenient to express the electron pressure (as given by the classical perfect-gas equation of state) in terms of ρ and β_e [cf. equation (7)], defined in the manner

$$p_e = \frac{k}{\mu_e H}\rho T = \frac{\beta_e}{1-\beta_e}\frac{1}{3}aT^4 \tag{47}$$

where p_e now denotes the electron pressure. Then, analogous to equation (9), we can write

$$p_e = \left[\left(\frac{k}{\mu_e H}\right)^4 \frac{3}{a}\frac{1-\beta_e}{\beta_e}\right]^{1/3} \rho^{4/3} \tag{48}$$

Comparing this with equation (42), we conclude that if

$$\left[\left(\frac{k}{\mu_e H}\right)^4 \frac{3}{a}\frac{1-\beta_e}{\beta_e}\right]^{1/3} > K_2 = \frac{1}{8}\left(\frac{3}{\pi}\right)^{1/3}\frac{hc}{(\mu_e H)^{4/3}} \tag{49}$$

the pressure p_e given by the classical perfect-gas equation of state will be greater than that given by the equation if degeneracy were to prevail, not only for the prescribed ρ and T, but for *all* ρ and T having the same β_e.

Inserting for a its value given in equation (13), we find that the inequality (49) reduces to

$$\frac{960}{\pi^4}\frac{1-\beta_e}{\beta_e} > 1 \tag{50}$$

or, equivalently,

$$1-\beta_e > 0.0921 = 1-\beta_\omega \tag{51}$$

(see Fig. 5).

For our present purposes, the principal content of the inequality (51) is the criterion that for a star to develop degeneracy it is necessary that the radiation pressure be less than 9.2 percent of (p_e+p_{rad}). This last inference is so central to all current schemes of stellar evolution that the directness and the simplicity of the early arguments are worth repeating.

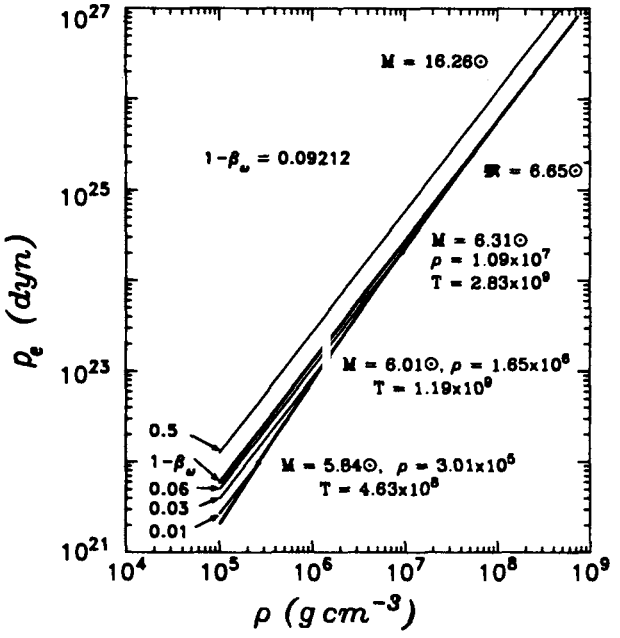

Fig. 5. Illustrating the onset of degeneracy for increasing density at constant β. Notice that there are no intersections for $1-\beta>0.09212$. In the figure, $1-\beta$ is converted into the mass of a star built on the standard model.

The two principal elements of the early arguments were these: *first,* that radiation pressure becomes increasingly dominant as the mass of the star increases; and *second,* that the degeneracy of electrons is possible only so long as the radiation pressure is not a significant fraction of the total pressure—indeed, as we have seen, it must not exceed 9.2 percent of (p_e+p_{rad}). The second of these elements in the arguments is a direct and an elementary consequence of the physics of degeneracy; but the first requires some amplification.

That radiation pressure must play an increasingly dominant role as the mass of the star increases is one of the earliest results in the study of stellar structure that was established by *Eddington.* A quantitative expression for this fact is given by *Eddington*'s *standard model* which lay at the base of his early studies summarized in his *The Internal Constitution of the Stars.*

On the standard model, the fraction β (=gas pressure/total pressure) is a constant through a star. On this assumption, the star is a polytrope of index 3 as is apparent from equation (9); and, in consequence, we have the relation [cf. equation (43)]

$$M=4\pi\left(\frac{C(\beta)}{\pi G}\right)^{3/2}(2.018) \tag{52}$$

where $C(\beta)$ is defined in equation (9). Equation (52) provides a quartic equation for β analogous to equation (17) for β_*. Equation (52) for $\beta=\beta_\omega$ gives

$$M=0.197\beta_\omega^{-3/2}\left(\frac{hc}{G}\right)^{3/2}\frac{1}{(\mu H)^2}=6.65\mu^{-2}\odot=\mathfrak{M} \tag{53}$$

On the standard model, then, stars with masses exceeding $\mathfrak{M}$ will have radiation pressures which exceed 9.2 percent of the total pressure. Consequently stars with $M>\mathfrak{M}$ cannot, at any stage during the course of their evolution, develop degeneracy in their interiors. Therefore, for such stars an eventual white-dwarf state is not possible unless they are able to eject a substantial fraction of their mass.

The standard model is, of course, only a model. Nevertheless, except under special circumstances, briefly noted below, experience has confirmed the essential qualitative correctness of the conclusions drawn from the standard model, namely that the evolution of stars of masses exceeding $7-8\odot$ must proceed along lines very different from those of less massive stars. These conclusions, which were arrived at some fifty years ago, appeared then so convincing that assertions such as these were made with confidence:

> Given an enclosure containing electrons and atomic nuclei (total charge zero) what happens if we go on compressing the material indefinitely? (1932)[10].
>
> The life history of a star of small mass must be essentially different from the life history of a star of large mass. For a star of small mass the natural white-dwarf stage is an initial step towards complete extinction. A star of large mass cannot pass into the white-dwarf stage and one is left speculating on other possibilities (1934)[8].

And these statements have retained their validity.

While the evolution of the massive stars was thus left uncertain, there was no such uncertainty regarding the final states of stars of sufficiently low mass[11]. The reason is that by virtue, again, of the inequality (10), the maximum central pressure attainable in a star must be less than that provided by the degenerate equation of state, so long as

$$\tfrac{1}{2}G(\tfrac{4}{3}\pi)^{1/3}M^{2/3}<K_2=\frac{1}{8}\left(\frac{3}{\pi}\right)^{1/3}\frac{hc}{(\mu_e H)^{4/3}} \tag{54}$$

or, equivalently

$$M<\frac{3}{16\pi}\left(\frac{hc}{G}\right)^{3/2}\frac{1}{(\mu_e H)^2}=1.74\mu_e^{-2}\odot \tag{55}$$

We conclude that there can be no surprises in the evolution of stars of mass less than $0.43\odot$ (if $\mu_e=2$). The end stage in the evolution of such stars can only be that of the white dwarfs. (Parenthetically, we may note here that the inequality (55) implies that the so-called "mini" black-holes of mass $\approx 10^{15}$ g cannot naturally be formed in the present astronomical universe.)

7. Some Brief Remarks on Recent Progress in the Evolution of Massive Stars and the Onset of Gravitational Collapse

It became clear, already from the early considerations, that the inability of the massive stars to become white dwarfs must result in the development of much more extreme conditions in their interiors and, eventually, in the onset of gravitational collapse attended by the super-nova phenomenon. But the precise manner in which all this will happen has been difficult to ascertain, in spite of great effort by several competent groups of investigators. The facts which must be taken into account appear to be the following[*].

In the first instance, the density and the temperature will steadily increase without the inhibiting effect of degeneracy since for the massive stars considered $1-\beta_e > 1-\beta_\omega$. On this account, "nuclear ignition" of carbon, say, will take place which will be attended by the emission of neutrinos. This emission of neutrinos will effect a cooling and a lowering of $(1-\beta_e)$; but it will still be in excess of $1-\beta_\omega$. The important point here is that the emission of neutrinos acts selectively in the central regions and is the cause of the lowering of $(1-\beta_e)$ in these regions. The density and the temperature will continue to increase till the next ignition of neon takes place followed by further emission of neutrinos and a further lowering of $(1-\beta_e)$. This succession of nuclear ignitions and lowering of $(1-\beta_e)$ will continue till $1-\beta_e < 1-\beta_\omega$ and a relativistically degenerate core with a mass approximately that of the limiting mass ($=1.4\odot$ for $\mu_e=2$) forms at the centre. By this stage, or soon afterwards, instability of some sort is expected to set in (see Section 8) followed by gravitational collapse and the phenomenon of the super-nova (of type II). In some instances, what was originally the highly relativistic degenerate core of approximately $1.4\odot$ will be left behind as a neutron star. That this happens sometimes is confirmed by the fact that in those cases for which reliable estimates of the masses of pulsars exist, they are consistently close to $1.4\odot$. However, in other instances—perhaps, in the majority of the instances—what is left behind, after all "the dust has settled", will have masses in excess of that allowed for stable neutron stars; and in these instances black holes will form.

In the case of less massive stars ($M \approx 6-8\odot$) the degenerate cores, which are initially formed, are not highly relativistic. But the mass of the core increases with the further burning of the nuclear fuel at the interface of the core and the mantle; and when the core reaches the limiting mass, an explosion occurs following instability; and it is believed that this is the cause underlying super-nova phenomenon of type I.

From the foregoing brief description of what may happen during the late stages in the evolution of massive stars, it is clear that the problems one encounters are of exceptional complexity, in which a great variety of physical factors compete. This is clearly not the occasion for me to enter into a detailed discussion of these various questions.

[*] I am grateful to Professor *D. Arnett* for guiding me through the recent literature and giving me advice in the writing of this section.

8. Instabilities of Relativistic Origin: (1) The Vibrational Instability of Spherical Stars

I now turn to the consideration of certain types of stellar instabilities which are derived from the effects of general relativity and which have no counterparts in the Newtonian framework. It will appear that these new types of instabilities of relativistic origin may have essential roles to play in discussions pertaining to gravitational collapse and the late stages in the evolution of massive stars.

We shall consider first the stability of spherical stars for purely radial perturbations. The criterion for such stability follows directly from the linearized equations governing the spherically symmetric radial oscillations of stars. In the framework of the Newtonian theory of gravitation, the stability for radial perturbations depends only on an average value of the adiabatic exponent, Γ_1, which is the ratio of the fractional Lagrangian changes in the pressure and in the density experienced by a fluid element following the motion; thus

$$\Delta P/P = \Gamma_1 \Delta\rho/\rho \tag{56}$$

And the Newtonian criterion for stability is

$$\bar{\Gamma}_1 = \int_0^M \Gamma_1(r) P(r)\, dM(r) \div \int_0^M P(r)\, dM(r) > \tfrac{4}{3} \tag{57}$$

If $\Gamma_1 < 4/3$, *dynamical instability* of a global character will ensue with an *e*-folding time measured by the time taken by a sound wave to travel from the centre to the surface.

When one examines the same problem in the framework of the general theory of relativity, one finds[12] that, again, the stability depends on an average value of Γ_1; but contrary to the Newtonian result, the stability now depends on the radius of the star as well. Thus, one finds that no matter how high $\bar{\Gamma}_1$ may be, instability will set in provided the radius is less than a certain determinate multiple of the *Schwarzschild radius*:

$$R_S = 2GM/c^2 \tag{58}$$

Thus, if for the sake of simplicity, we assume that Γ_1 is a constant through the star and equal to 5/3, then the star will become dynamically unstable for radial perturbations, if $R_1 < 2.4 R_S$. And further, if $\Gamma_1 \to \infty$, instability will set in for all $R < (9/8) R_S$. *The radius* $(9/8) R_S$ *defines, in fact, the minimum radius which any gravitating mass, in hydrostatic equilibrium, can have in the framework of general relativity.* This important result is implicit in a fundamental paper by *Karl Schwarzschild* published in 1916. (*Schwarzschild* actually proved that for a star in which the energy density is a uniform $R > (9/8) R_S$.)

In one sense, the most important consequence of this instability of relativistic origin is that if Γ_1 (again assumed to be a constant for the sake of simplicity) differs from and is greater than 4/3 only by a small positive constant, then the instability will set in for a radius R which is a large multiple of R_S; and, therefore, under circumstances when the effects of general relativity, on the structure of the equilibrium configuration itself, are hardly relevant. Indeed, it

follows[13] from the equations governing radial oscillations of a star, in a first post-Newtonian approximation to the general theory of relativity, that instability for radial perturbations will set in for all

$$R < \frac{K}{\Gamma_1 - 4/3}\frac{2GM}{c^2} \tag{59}$$

where K is a constant which depends on the *entire*[*] march of density and pressure in the equilibrium configuration in the Newtonian framework. Thus, for a polytrope of index n, the value of the constant is given by

$$K = \frac{5-n}{18}\left[\frac{2(11-n)}{(n+1)\xi_1^4|\theta_1'|^3}\int_0^{\xi_1}\theta\left(\frac{d\theta}{d\xi}\right)^2\xi^2 d\xi + 1\right] \tag{60}$$

where θ is the Lane-Emden function in its standard normalization ($\theta = 1$ at $\xi = 0$), ξ is the dimensionless radial coordinate, ξ_1 defines the boundary of the polytrope (where $\theta = 0$) and θ_1' is the derivative of θ at ξ_1.

Table 2. Values of the constant K in the inequality (59) for various polytropic indices, n.

n	K	n	K
0	0.452381	3.25	1.28503
1.0	0.565382	3.5	1.49953
1.5	0.645063	4.0	2.25338
2.0	0.751296	4.5	4.5303
2.5	0.900302	4.9	22.906
3.0	1.12447	4.95	45.94

In Table 2, we list the values of K for different polytropic indices. It should be particularly noted that K increases without limit as $n \to 5$ and the configuration becomes increasingly centrally condensed[**]. Thus, already for $n = 4.95$ (for which polytropic index $\rho_c = 8.09 \times 10^6 \bar{\rho}$), $K \sim 46$. In other words, for the highly centrally condensed massive stars (for which Γ_1 may differ from 4/3 by as little as 0.01)[***], the instability of relativistic origin will set in, already, when its radius falls below $5 \times 10^3 R_S$. Clearly this relativistic instability must be considered in the contexts of these problems.

A further application of the result described in the preceding paragraph is to degenerate configurations near the limiting mass[14]. Since the electrons in these highly relativistic configurations have velocities close to the velocity of light, the effective value of Γ_1 will be very close to 4/3 and the post-Newtonian relativistic instability will set in for a mass slightly less than that of the limiting mass. On account of the instability for radial oscillations setting in for a mass less than M_{limit}, the period of oscillation, along the sequence of the degenerate configurations, must have a minimum. This minimum can be estimated to be about two seconds (see Fig. 6). Since pulsars, when they were discovered, were known to have periods much less than this minimum value, the possibility of their being degenerate configurations near the limiting mass was ruled out; and this was one of the deciding factors in favor of the pulsars being neutron stars. (But by a strange irony, for reasons we have briefly explained in Section 7, pulsars which have resulted from super-nova explosions have masses close to $1.4\,\odot$!)

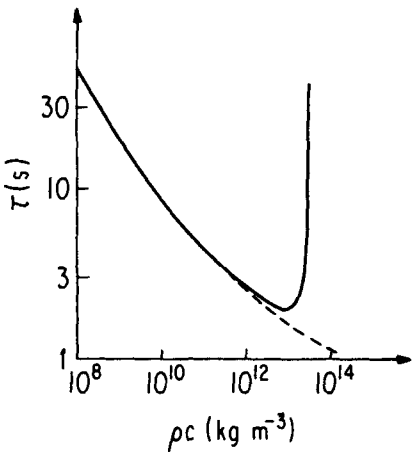

Fig. 6. The variation of the period of radial oscillation along the completely degenerate configurations. Notice that the period tends to infinity for a mass close to the limiting mass. There is consequently a minimum period of oscillation along these configurations; and the minimum period is approximately 2 seconds. (From J. Skilling: *Pulsating Stars*, Plenum Press, New York 1968, p. 59.)

Finally, we may note that the radial instability of relativistic origin is the underlying cause for the *existence* of a maximum mass for stability: it is a direct consequence of the equations governing hydrostatic equilibrium in general relativity. (For a complete investigation on the periods of radial oscillation of neutron stars for various admissible equations of state, see a recent paper by *Detweiler* and *Lindblom*[15].)

9. Instabilities of Relativistic Origin: (2) The Secular Instability of Rotating Stars Derived from the Emission of Gravitational Radiation by Non-Axisymmetric Modes of Oscillation

I now turn to a different type of instability which the general theory of relativity predicts for rotating configurations. This new type of instability[16] has its origin in the fact that the general theory of relativity builds into rotating masses a dissipative mechanism derived from the possibility of the emission of gravitational radiation by non-axisymmetric modes of oscillation. It appears that this insta-

[*] It is for this reason that we describe the instability as *global*.

[**] Since this was written, it has been possible to show (Chandrasekhar and Lebovitz, *Mon. Not. R. Astron. Soc. 207* (1984) 13P) that for $n \to 5$, the asymptotic behavior of K is given by

$$K \to 2.3056/(5-n)$$

and, further, that along the polytropic sequence, the criterion for instability (59) can be expressed alternatively in the form

$$R < 0.2264\left(\frac{\rho_c}{\bar{\rho}}\right)^{1/3}\frac{2GM}{c^2}\frac{1}{\Gamma_1 - 4/3}\quad(\rho_c/\bar{\rho} \gtrsim 10^6).$$

[***] By reason of the dominance of the radiation pressure in these massive stars and of β being very close to zero.

bility limits the periods of rotation of pulsars. But first, I shall explain the nature and the origin of this type of instability.

It is well known that a possible sequence of equilibrium figures of rotating homogeneous masses is the Maclaurin sequence of oblate spheroids[17]. When one examines the second harmonic oscillations of the Maclaurin spheroid, in a frame of reference rotating with its angular velocity, one finds that for two of these modes, whose dependence on the azimuthal angle is given by $e^{2i\varphi}$, the characteristic frequencies of oscillation, σ, depend on the eccentricity e in the manner illustrated in Figure 7. It will be observed that

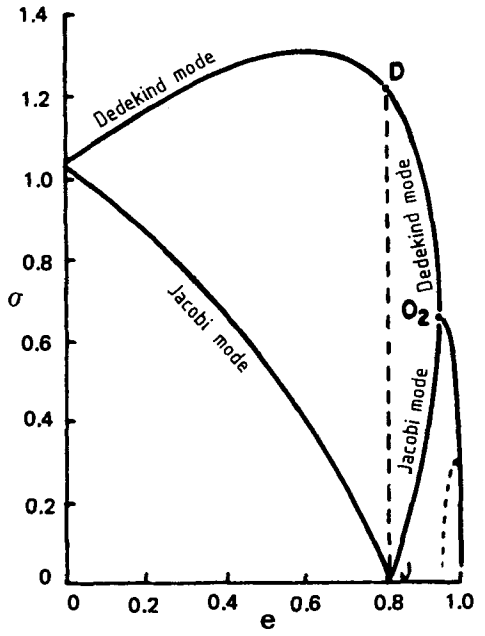

Fig. 7. The characteristic frequencies (in units of $(\pi G\rho)^{1/2}$) of the two even modes of second-harmonic oscillation of the Maclaurin spheroid. The Jacobi sequence bifurcates from the Maclaurin sequence by the mode that is neutral ($\sigma=0$) at $e=0.813$; and the Dedekind sequence bifurcates by the alternative mode at D. At O_2 ($e=0.9529$) the Maclaurin spheroid becomes dynamically unstable. The real and the imaginary parts of the frequency, beyond O_2, are shown by the full line and the dashed curves, respectively. Viscous dissipation induces instability in the branch of the Jacobi mode; and radiation-reaction induces instability in the branch DO_2 of the Dedekind mode.

one of these modes becomes neutral (i.e., $\sigma=0$) when $e=0.813$ and that the two modes coalesce when $e=0.953$ and become complex conjugates of one another beyond this point. Accordingly, the Maclaurin spheroid becomes *dynamically unstable* at the latter point (first isolated by *Riemann*). On the other hand, the origin of the neutral mode at $e=0.813$ is that at this point a new equilibrium sequence of triaxial ellipsoids—the ellipsoids of Jacobi—bifurcate. On this latter account, *Lord Kelvin* conjectured in 1883 that:

> if there be any viscosity, however slight ... the equilibrium beyond $e=0.81$ cannot be secularly stable.

Kelvin's reasoning was this: viscosity dissipates energy but not angular momentum. And since for equal angular momenta, the Jacobi ellipsoid has a lower energy content than the Maclaurin spheroid, one may expect that the action of viscosity will be to dissipate the excess energy of the Maclaurin spheroid and transform it into the Jacobi ellipsoid with the lower energy. A detailed calculation[18] of the effect of viscous dissipation on the two modes of oscillation, illustrated in Figure 7, does confirm *Lord Kelvin*'s conjecture. It is found that viscous dissipation makes the mode, which becomes neutral at $e=0.813$, unstable beyond this point with an e-folding time which depends inversely on the magnitude of the kinematic viscosity and which further decreases monotonically to zero at the point $e=0.953$, where the dynamical instability sets in.

Since the emission of gravitational radiation dissipates *both* energy and angular momentum, it does *not* induce instability in the Jacobi mode; instead it induces instability in the *alternative* mode at the same eccentricity. In the first instance this may appear surprising; but the situation we encounter here clarifies some important issues.

If instead of analyzing the normal modes in the rotating frame, we had analyzed them in the inertial frame, we would have found that the mode which becomes unstable by radiation reaction at $e=0.813$, is in fact neutral at this point. And the neutrality of *this* mode in the inertial frame corresponds to the fact that the neutral deformation at this point is associated with the bifurcation (at this point) of a new triaxial sequence—the sequence of the Dedekind ellipsoids. These Dedekind ellipsoids, while they are congruent to the Jacobi ellipsoids, they differ from them in that they are at rest in the inertial frame and owe their triaxial figures to internal vertical motions. An important conclusion that would appear to follow from these facts is that in the framework of general relativity we can expect secular instability, derived from radiation-reaction to arise from a Dedekind mode of deformation (which is quasi-stationary in the inertial frame) rather than the Jacobi mode (which is quasi-stationary in the rotating frame).

A further fact concerning the secular instability induced by radiation-reaction, discovered subsequently by *Friedman*[19] and by *Comins*[20], is that the modes belonging to higher values of m ($=3, 4, \ldots$) become unstable at smaller eccentricities, though the e-folding times for the instability become rapidly longer. Nevertheless, it appears from some preliminary calculations of *Friedman*[21] that it is the secular instability derived from modes belonging to $m=3$ (or 4) that limit the periods of rotation of the pulsars.

It is clear from the foregoing discussions that the two types of instabilities of relativistic origin we have discussed are destined to play significant roles in the contexts we have considered.

10. The Mathematical Theory of Black Holes

So far, I have considered only the restrictions on the last stages of stellar evolution that follow from the existence of an upper limit to the mass of completely degenerate configurations and from the instabilities of relativistic origin. From these and related considerations, the conclusion is inescapable that black holes will form as one of the natural end products of stellar evolution of massive stars; and further that they must exist in large numbers in the present astronomical universe. In this last section I want to consider

very briefly what the general theory of relativity has to say about them. But first, I must define precisely what a black hole is.

A black hole partitions three-dimensional space into two regions: an inner region which is bounded by a smooth two-dimensional surface called the *event horizon*; and an outer region, external to the event horizon, which is asymptotically flat; and it is required (as a part of the definition) that no point in the inner region can communicate with any point of the outer region. This incommunicability is guaranteed by the impossibility of any light signal, originating in the inner region, crossing the event horizon. The requirement of asymptotic flatness of the outer region is equivalent to the requirement that the black hole is isolated in space and that far from the event horizon the space-time approaches the customary space-time of terrestrial physics.

In the general theory of relativity, we must seek solutions of *Einstein*'s vacuum equations compatible with the two requirements I have stated. It is a startling fact that compatible with these very simple and necessary requirements, the general theory of relativity allows for stationary (i.e., time-independent) black-holes exactly a single, unique, two-parameter family of solutions. This is the Kerr family, in which the two parameters are the mass of the black hole and the angular momentum of the black hole. What is even more remarkable, the metric describing these solutions is simple and can be explicitly written down.

I do not know if the full import of what I have said is clear. Let me explain.

Black holes are macroscopic objects with masses varying from a few solar masses to millions of solar masses. To the extent they may be considered as stationary and isolated, to that extent, they are all, every single one of them, described *exactly* by the Kerr solution. This is the only instance we have of an exact description of a macroscopic object. Macroscopic objects, as we see them all around us, are governed by a variety of forces, derived from a variety of approximations to a variety of physical theories. In contrast, the only elements in the construction of black holes are our basic concepts of space and time. They are, thus, almost by definition, the most perfect macroscopic objects there are in the universe. And since the general theory of relativity provides a single unique two-parameter family of solutions for their descriptions, they are the simplest objects as well.

Turning to the physical properties of the black holes, we can study them best by examining their reaction to external perturbations such as the incidence of waves of different sorts. Such studies reveal an analytic richness of the Kerr space-time which one could hardly have expected. This is not the occasion to elaborate on these technical matters[22]. Let it suffice to say that, contrary to every prior expectation, all the standard equations of mathematical physics can be solved exactly in the Kerr space-time. And the solutions predict a variety and range of physical phenomena which black holes must exhibit in their interaction with the world outside.

The mathematical theory of black holes is a subject of immense complexity. But its study has convinced me of the basic truth of the ancient mottoes:

The simple is the seal of the true

and

Beauty is the splendour of truth.

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Organic Polymeric and Non-Polymeric Materials with Large Optical Nonlinearities

By David J. Williams

Nonlinear optical properties are a sensitive probe of the electronic and solid-state structure of organic compounds and as a consequence find various applications in many areas of optoelectronics including optical communications, laser scanning and control functions, and integrated optics technology. Because of their strongly delocalized π electronic systems, polymeric and non-polymeric aromatic compounds show highly nonlinear optical effects. Nowadays, polymer chemists are able to tailor specific materials properties for various applications. Some organic substances with π electronic systems exhibit the largest known nonlinear coefficients, often considerably larger than those of the more conventional inorganic dielectrics and semiconductors, and thus show promise for thin-film fabrication, allowing the enormous function and cost advantages of integrated electronic circuitry. The electronic origins of nonlinear optical effects in organic π electronic systems are reviewed, with special emphasis being given to second-order nonlinear optical effects. Methods for measuring nonlinear optical responses are outlined, and the critical relationships of the propagation characteristics of light to observed nonlinear optical effects and to solid-state structure are discussed. Finally, the synthesis and characterization of organic crystals and polymer films with large second-order optical nonlinearities are summarized.

1. Introduction

Interest in nonlinear optics has grown tremendously in recent years, primarily because of the telecommunications industry's need for high-bandwidth optical switching and processing devices to service the information and data transmission needs of the computer age, and of the proliferation of sophisticated laser tools, which has nurtured and necessitated research on new methods for tailoring individual laser pulses to perform specific functions or be readily detected in complex experiments.

Nonlinear optics is concerned with the interactions of electromagnetic fields in various media to produce new fields altered in phase, frequency, amplitude, or other propagation characteristics from the incident fields. The media in which these effects occur are becoming the subject of intense interest, since their adjunct properties (stability, ease of preparation, compatibility with microelectronic processing methods, adhesion, mechanical, and other properties) as well as their nonlinear optical properties will ultimately determine the technological utility of the effect.

The origin of nonlinear optical effects will be described here in a phenomenological manner, and several specific effects and their experimental detection and characterization will be described in some detail. Recent efforts in chemical research have been aimed at achieving large second-order nonlinear responses in organic and polymeric materials[1], and several of these will be reviewed.

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1.1. Nonlinearity of a Molecular Dielectric Response

In order to gain an insight into the origin of nonlinear optical effects, the polarization P induced in a molecule by a local electric field E is expanded in powers of the electric field [Eq. (1)].

$$P = \alpha E + \beta E^2 + \gamma E^3 + \cdots \quad (1)$$

For the moment, it will be assumed that the polarization is a scalar quantity (as opposed to a vector). The first term α in the expansion is the familiar linear polarization and is the origin of the refractive index if the field E is associated with an electromagnetic wave in the optical frequency range. The coefficients are actually complex numbers, the real part in α corresponding to the index of refraction and the imaginary part to absorption of a photon by the molecule. When an electromagnetic field interacts with a molecule or a medium consisting of many molecules, the field polarizes the molecules. These, in turn, act as oscillating dipoles broadcasting electromagnetic radiation, which can then be detected at some point in space outside of the medium. In a nonlinear medium the induced polarization is a nonlinear function of the applied field. This is illustrated in Figure 1 for a medium where the first nonlinear term β makes a significant contribution to the induced-frequency components. In this example the medium exhibits an asymmetric nonlinear response to the applied field $E(\omega)$. A medium exhibiting such a response might consist of a crystal composed of molecules with asymmetric charge distributions, as shown, arranged in the crystal in such a way that a polar orientation is maintained throughout the crystal. From chemical intuition it is clear that the molecules are more easily polarized in the direction from the elec-

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tron-rich substituent D (donor) to electron-deficient substituent A (acceptor).

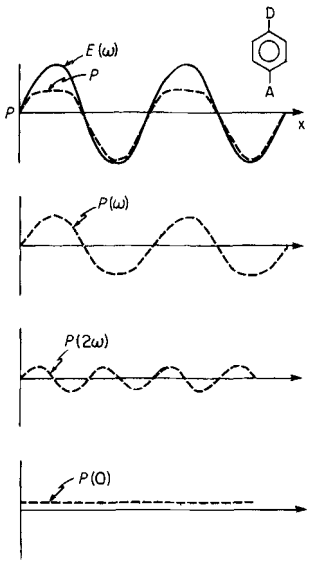


Fig. 1. Top: Plot of the polarization response P to an incident electromagnetic wave of field strength $E(\omega)$ at frequency ω in a noncentrosymmetric medium. Bottom: Fourier components of P at frequencies ω, 2ω, and 0. See also text.

An important general statement can now be made regarding β. If the molecule (or medium in the illustration) is centrosymmetric, then $\beta \equiv 0$. This can be readily seen by the following argument. If a field $+E$ is applied to the molecule (medium), Equation (1) predicts that the polarization induced by the first nonlinear term is $+\beta E^2$. If a field $-E$ is applied, the polarization is still predicted to be $+\beta E^2$, yet if the medium is centrosymmetric the polarization should be $-\beta E^2$. This contradiction can be resolved only if $\beta \equiv 0$ in centrosymmetric media. If we use the same arguments for the next higher order term, $+E$ produces polarization $+\gamma E^3$ and $-E$ produces $-\gamma E^3$ so that γ is the first nonzero nonlinear term in centrosymmetric media.

Referring to Figure 1 again, the Fourier theorem states that a nonsinusoidal periodic response such as P can be described by the sum of a series of sinusoidal functions with appropriate coefficients of harmonics of the fundamental frequency ω[2]. If this response P is asymmetric, an appropriate summation of the even harmonics (the Fourier components consisting of sinusoidal functions of the harmonics 0, 2ω, 4ω, 6ω, etc.) describe the function P. If the nonlinear response is symmetric, however, the odd terms ω, 3ω, 5ω, etc. describe the response. Figure 2 shows an example of a nonlinear response in a centrosymmetric medium such as benzene, where the polarizable π system is responsible for the symmetric nonlinear polarization. The Fourier decomposition would consist of responses at ω, 3ω, 5ω, etc. with progressively decreasing amplitudes (coefficients) of the higher order components. As the incident field $E(\omega)$ in either example becomes more intense, the nonlinear terms contribute more significantly.

Noncentrosymmetric crystals can exhibit harmonic generation (2ω) or frequency doubling (SHG, second harmonic generation), i.e. conversion of coherent light of frequency ω into light frequency 2ω, and optical rectification, i.e. the ability to induce a DC voltage between electrodes placed on the surface of the crystal when an intense laser beam is directed into the crystal. On the other hand, liquids such as benzene or vapors of a polarizable medium exhibit a light intensity dependent refractive index (ω), third-harmonic generation (3ω), and fifth- or higher order harmonics for very intense laser beams in certain metal vapors.

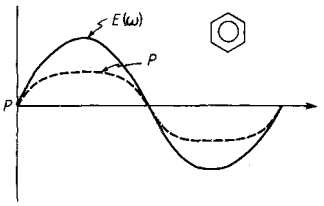


Fig. 2. Plot of the nonlinear polarization response P to an incident electromagnetic field in a centrosymmetric medium.

Another example of a second-order nonlinear optical effect is the linear electro-optic or Pockels effect. Here a DC field is applied to a medium through which an optical wave propagates. Once again this effect arises through β, but the polarization now has a contribution arising from $E(0)E(\omega)$ rather than $E(\omega)^2$ as in second-harmonic generation. The change in polarization due to the presence of these two interacting field components effectively alters the refractive index of the medium η, giving it a field dependence $\eta(E)$.

1.2. Microscopic Nonlinearities

The intuitive description of nonlinear optical processes in Section 1.1 could be extended to additional nonlinear effects, but many of the important aspects and consequences of nonlinear optics cannot be discussed without putting the effects on a more rigorous physical basis. In this section the constitutive relationships will be precisely stated and the reader will be referred to some of the treatises on the subject for additional background.

The polarization induced in a molecule by an applied electric field is

$$P_i = \alpha_{ij}E_j + \beta_{ijk}E_{jk} + \gamma_{ijkl}E_jE_kE_l + \cdots \quad (2)$$

where the subscripts i, j, k, l refer to the molecular coordinate system and E_j, E_{jk}, etc. denote the components of the applied field[3]. Rather than being scalar quantities as expressed in Equation (1), it is obvious that the induced polarization in a molecule is a vector and is related to the electric-field vectors through the components of the tensor coefficients. The third-rank tensor β_{ijk} has properties similar to a vector[4], but γ, a fourth-rank tensor, has the properties of a scalar. This can be seen more readily by relating the values of β and γ obtained in experimental measurements to the components of the tensors [Eqs. (3) and (4)].

$$\beta = \beta_{zxx} + \beta_{zyy} + \beta_{zzz} \quad (3)$$

$$\gamma = 1/5(\gamma_{xxxx} + \gamma_{yyyy} + \gamma_{zzzz} + 2\gamma_{xxyy} + 2\gamma_{xxzz} + 2\gamma_{yyzz}) \quad (4)$$

Recalling that the indices indicate the projection of field components in the direction indicated by the second two indices, ($\beta_{z\underline{xx}}$) on the molecular axis indicated by the first index ($\beta_{\underline{z}xx}$), the vectorial nature of β for fixed molecular and field directions is clear. Referring to Figure 3, where the z axis of the molecule is designated as passing through the carbon atoms to which the electron-rich substituent D (donor) and electron-deficient substituent A (acceptor) are attached, it is clear that the components of the arbitrarily chosen field direction will polarize the molecule most strongly in the z direction. If we devise an experiment where the applied field is pointed in the direction of the molecular z axis, it is clear that β_{zzz} will be the dominant contributor to the nonlinear response. γ, on the other hand, has the characteristics of a scalar with field projections contributing in all molecular directions. To demonstrate these points, an analysis of the properties of even- and odd-rank tensors is required[4].

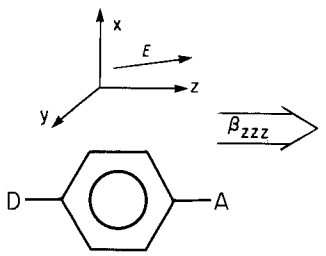


Fig. 3. Organic compound with electron-rich (donor) and -deficient (acceptor) substituents which provide the asymmetric charge distribution in the π system required for large β. Also shown is a reference coordinate system with z parallel to the dipolar axis of the molecule. Since the molecule is most easily polarized for field components parallel to the z axis, β_{zzz} is the largest component of the β_{ijk} tensor.

1.3. Macroscopic Nonlinearities

Nonlinear optical properties are measured on macroscopic samples that consist of many individual molecules. Although it is possible to infer the values of the molecular hyperpolarizabilities from measurements on macroscopic samples, great care must be taken to determine the values of the *internal* electric fields, and the propagation characteristics of the generated fields must be carefully considered[5].

The polarization induced in a medium by an external electric field is given by Equation (5)[6].

$$P=\chi^{(1)}E+\chi^{(2)}E^2+\chi^{(3)}E^3+\cdots \tag{5}$$

E is the applied field and the $\chi^{(n)}$ have meanings similar to the molecular coefficients in Equation (2). The odd-order coefficients $\chi^{(1)}, \chi^{(3)}, \ldots$ are readily related to the molecular properties by Equations (6) and (7)[7].

$$\chi^{(1)}=N\alpha F(\omega) \tag{6}$$
$$\chi^{(3)}=N\gamma F(\omega_1)F(\omega_2)F(\omega_3)F(\omega_4) \tag{7}$$

N is the number of molecules per unit volume and F is a local field factor at frequency ω which determines the value of the electric field at the site of the molecule[7]. The even-order coefficients $\chi^{(2)}$ require a detailed knowledge of the projection of the molecular hyperpolarizability tensors onto the unit cell of the noncentrosymmetric crystal containing that molecule. Here, therefore, we will only state the relationship for the simplest possible case, a rigid lattice-oriented gas[8] (all molecules pointing in the same direction and fixed in space).

$$\chi^{(2)}=N\beta F(\omega_1)F(\omega_2)F(\omega_3) \tag{8}$$

The field factors for nonassociating liquids which were determined by *Onsager*[9,10] are generally used in these expressions [Eq. (9)].

$$F(\omega_i)=(\varepsilon_\infty^i+2)\varepsilon_\omega/(\varepsilon_\infty^i+2\varepsilon_\omega) \tag{9}$$

Zyss and *Oudar*[11,12] recently analyzed the relation between β and $\chi^{(2)}$ for molecules in various space groups and showed that polar molecules that crystallize in the 1, 2, m, and mm2 point groups have the largest potential nonlinear coefficients and that within those point groups the orientation of the molecule is critical.

The coefficient $\chi^{(2)}$ is used below to illustrate several further points about the nature of the induced nonlinear polarization. The coefficient is often written as

$$\chi^{(2)}_{ijk}(-\omega_3;\omega_2,\omega_1) \tag{10}$$

where i, j, k refer to the principal axes of the medium and indicate the tensorial characteristics of $\chi^{(2)}$. The frequency arguments indicate the frequency of the resultant field ω_3 for input frequencies ω_2, ω_1. The minus sign is a convention indicating momentum conservation given by the vector sum

$$k_3+k_2+k_1=0 \tag{11}$$

where k_i (i = 1, 2, 3) is the wave vector given by $k_i=2\pi/\lambda_i$ and points in the direction of propagation of the wave. Thus, for second-harmonic generation the expression (10) would be written $\chi^{(2)}_{ijk}(-2\omega;\omega,\omega)$, and for the linear electro-optic (Pockels) effect $\chi^{(2)}_{ijk}(-\omega;0,\omega)$. A variety of nonlinear optical effects can occur through $\chi^{(2)}$ and $\chi^{(3)}$, depending on the exact nature of the input frequencies, the proximity of molecular vibrational or electronic resonances to the input frequencies or frequency combinations, and the phase-matching conditions, as indicated by Equation (11) and similar equations for $\chi^{(3)}$. A wide variety of conditions can lead to interesting nonlinear effects. Various susceptibility functions and frequency arguments are listed in Table 1 for $\chi^{(2)}$ and $\chi^{(3)}$.

Several comments are warranted concerning the information in the table. Since the incident field components can be in or out of phase with the natural electronic oscillations of the molecules constituting the nonlinear medium, χ is a complex number. Most of the effects listed and all of those discussed thus far occur through the real part Re(χ). The phenomenon of two-photon absorption occurs through the imaginary part Im($\chi^{(3)}$). It is beyond the scope of any single article to discuss the myriad of nonlinear effects occurring through $\chi^{(2)}$ and $\chi^{(3)}$[13-19]. In the fol-

Table 1. Electric susceptibility functions $\chi^{(2)}$, $\chi^{(3)}$ for various types of interacting field components (frequency arguments explained in text), terminology used for the effect, and known applications.

Susceptibility	Effect	Application
$\chi^{(2)}(0;\omega,-\omega)$	optical rectification	hybrid bistable device [13]
$\chi^{(2)}(-\omega;\omega,0)$	electro-optic (Pockels) effect	modulators [14], variable phase retarders
$\chi^{(2)}(-2\omega;\omega,\omega)$	frequency doubling	harmonic generation [15]
$\chi^{(2)}(-\omega_0;\omega_a,\omega_b)$	frequency mixing	parametric amplifiers [16], I. R. up convertors
$\chi^{(3)}(0;0,0,0)$	dielectric saturation	poling
$\chi^{(3)}(0;0,-\omega,\omega)$	second-order optical rectification	—
$\chi^{(3)}(-\omega;\omega,0,0)$	quadratic electro-optic effect	variable phase retardation, liquid-crystal displays
$\chi^{(3)}(-\omega_0;\omega_a,\omega_b,-\omega_b)$	AC electro-optic effect AC Kerr effect Brillouin scattering Raman scattering	high-speed optical gates [17]
$\mathrm{Im}(\chi^{(3)})(-\omega_a;\omega_0,\omega_b,-\omega_b)$	two-photon adsorption	—
$\chi^{(3)}(-\omega;\omega,\omega,-\omega)$	AC electro-optic effect AC Kerr effect self-focusing degenerate four-wave mixing	optical bistability [18], phase conjugation [19] (image processing), real-time holography, optical transistors
$\chi^{(3)}(-3\omega;\omega,\omega,\omega)$	frequency tripling	deep UV conversion

lowing, we will merely concern ourselves with the origin and characterization of β and $\chi^{(2)}$ in organic materials.

2. Experimental Methods

2.1. Determination of β

From a chemical point of view, one aim of research in nonlinear optics might be to synthesize materials with useful nonlinear optical and other properties for specific applications. Characterization of β of the constituent molecules is essential for a structure-property based understanding of molecules. A technique has been developed for measuring β without necessitating the incorporation of the molecule into noncentrosymmetric crystal structures. In this technique, called electric-field-induced second-harmonic generation (EFISH), a strong DC electric field is applied to a liquid or a solution of the molecules of interest in order to remove the orientational averaging by statistical alignment of molecular dipoles in the medium[4]. The induced second-order nonlinearity can then produce a signal at 2ω, from which β can be extracted[20–23].

Figure 4 shows schematically the essential elements of an EFISH experiment[5,22–24]. The 1.06 μm output of a Nd^{3+}: YAG laser is split and directed into a sample and a reference cell. The sample cell (Fig. 5) is translated by a stepper-motor-controlled stage across the beam. The laser pulse is synchronized with a high-voltage DC pulse to induce harmonic generation in the cell. The 0.53 μm radiation is separated from the 1.06 μm pump beam by filters and a monochromator, and the harmonic intensity is detected by a photomultiplier tube. The signal-to-noise ratio can be improved with a boxcar averager. The reference beam is directed into a crystal such as quartz, whose sec-

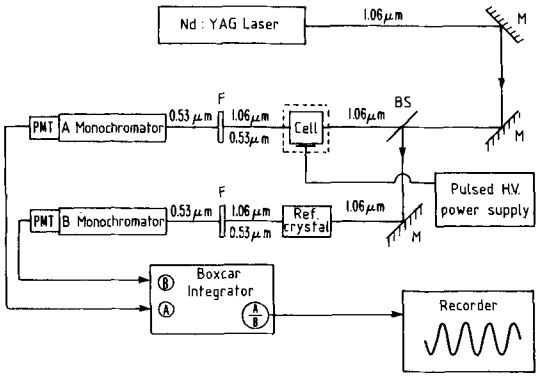


Fig. 4. Schematic diagram of an experimental system for measurement of β by the EFISH (electric-field-induced second-harmonic-generation) technique [24, 25]. M = mirror, BS = beam splitter, F = filters, PMT = photomultiplier tube. Lens and timing pulses are not shown.

ond-order properties are well known, so that fluctuations in beam intensity can be readily corrected in the output data. The value of the nonlinear coefficient is obtained from the ratio of the signals of the sample cell and a reference material such as quartz or $LiNbO_3$ with known $\chi^{(2)}$ [Eq. (12)].

$$\frac{l_{c(\text{sample})}}{l_{c(\text{reference})}}\left[\frac{\chi^{(2)}_{\text{sample}}}{\chi^{(2)}_{\text{reference}}}\right]^2 \propto \frac{I(2\omega)_{\text{sample}}}{I(2\omega)_{\text{reference}}} \tag{12}$$

l_c = the coherence length (see Fig. 6).

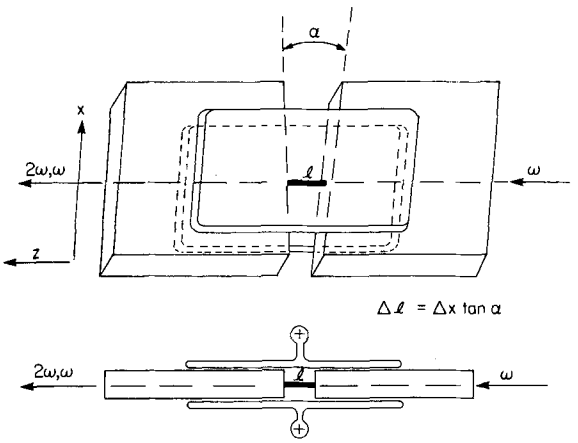


Fig. 5. Top view (above) and edge view (below) of a cell used for EFISH measurements. The glass is ca. 3 mm thick and ca. 1 cm long. The gap in which the liquid is confined is 1–2 mm, and the electrodes extend about five times the gap spacing to avoid nonuniform electric fields at the glass-liquid interface. The cell is translated in the x direction with respect to the beam to produce the fringes described in Figure 6.

The geometry of the sample cell is shown in greater detail in Figure 5. The cell consists of two glass rectangles set at an angle α with respect to each other (Fig. 5, top). Electrodes are placed above and below the glass surfaces (Fig.

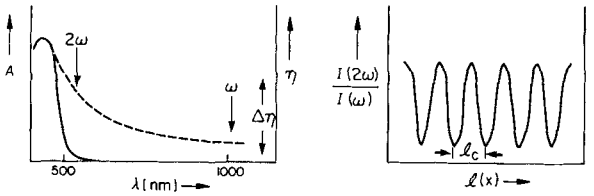


Fig. 6. Left: Schematic of an absorption band A (unbroken line) and dispersive refractive index (η, broken line) as a function of the wavelength λ for a typical aromatic ring system. The phase retardation ($\Delta\phi$) for light at the fundamental frequency ω and harmonic 2ω is determined by the dispersion in the refractive index ($\Delta\eta$) and the path length travelled (l) (c = speed of light).

$$\Delta\phi = \frac{\omega l}{c}\Delta\eta$$

For $\Delta\phi = 0$, $I(2\omega)/I(\omega)$ is a maximum; for $\Delta\phi = \pi/2$ the same expression is a minimum. Right: Ratio of harmonic to fundamental intensity when the path length refractive index discontinuities (boundaries of the cell in Fig. 5) is varied in the x direction. The harmonic conversion depends on the phases of the electric fields and thus also on the path length.

5, bottom), and the liquid to be measured is poured into the wedge-shaped gap between the glass pieces. Translation of the cell in the x direction produces a path length variation Δl depending on the distance traversed. The need for the wedge geometry and translation of the cell is best understood by referring to Figure 6. The left-hand side of the figure shows the wavelength dependence of the refractive index η and the absorption A for an aromatic molecule at the fundamental and harmonic frequencies. A convenient representation of the electric field associated with a light wave is given by Equation (13):

$$E(z) = E_0 e^{i(\omega t - \phi(z))} + c.c \tag{13}$$

E_0 is the amplitude, ω is the frequency, and $\phi(z)$ is a phase angle. Since the difference in the refractive index $\Delta\eta$ at ω and 2ω generates a phase-angle difference $\Delta\phi$, which is also a function of the distance traversed $l(z)$, the fundamental and harmonic fields will change their relative phases over some characteristic distance l_c. Since the flow of energy from fundamental to harmonic field or harmonic to fundamental field is a phase-sensitive process, we would expect to see oscillations in the harmonic intensity as the beam traverses the wedged cell with a defined characteristic coherence length l_c (Fig. 6, right). The intensity distribution between fundamental and harmonic is determined solely by the phase relationships that exist at the last liquid/glass boundary. *Oudar*[25] analyzed the propagation of the various waves in a nonlinear medium with the boundary conditions of the liquid cell. In the absence of optical absorption, the functional dependence $I(2\omega)/I(\omega)$ is expressed in terms of Equations (14a) and (14b).

$$I(2\omega)/I(\omega) = D + K\sin^2\psi \tag{14a}$$

$$\psi = -\frac{\omega}{2c} l\Delta\eta \tag{14b}$$

D and K are calibration factors[24,25].

The "nonphase-matched" wedge technique can be extended to all nonlinear media (liquids, films, crystals), as long as the sample can be shaped into a wedge or otherwise manipulated to produce a periodic phase-matched condition. The reference sample in Figure 4 could, for example, be a polished quartz crystal with a wedge cut perpendicular to the direction of largest nonlinearity.

In order to relate the experimental data obtained from the EFISH measurement to β, it is necessary to consider the expressions for microscopic and macroscopic nonlinearities. Since the experiment generates a harmonic field at 2ω from the interaction of three waves (two optical field components (E^{ω}) and a DC field component (E^0)), the induced nonlinear polarization must arise from a third-order nonlinear process

$$P^{2\omega} = \Gamma_{ijkl} E^{\omega} E^{\omega} E^0 \tag{15}$$

where

$$\Gamma_{ijkl} = \chi^{(3)}(-2\omega;\omega,\omega,0)$$

We can define an effective second-order coefficient

$$d_{ijk} = \Gamma_{ijkl} E_l \tag{16}$$

so that

$$P^{2\omega} = d_{ijk} \cdot E^{\omega} \cdot E^{\omega} \tag{17}$$

resembles a second-order nonlinear optical effect. For a pure liquid we can define a microscopic hyperpolarizability

$$\Gamma = NF\gamma^0 \tag{18}$$

where N is the density of molecules, and F is a local field correction $EF(\omega_i) = F$ (the internal field). The relationship of γ^0 to the hyperpolarizabilities of the molecules β_{ijk} and γ_{ijkl} requires a statistical analysis[26], and the result is

$$\gamma^0 = \gamma + \frac{\mu_z\beta_z}{5kT} \tag{19}$$

where the z axis is aligned with the dipole moment of the molecule. For conjugated organic systems $\mu_z\beta_z/5kT \gg \gamma$, so that with this analysis β has been obtained for a wide variety of organic molecules.

$$[I(2\omega)]^{1/2} \propto NF\frac{\mu_z\beta_z E^0}{5kT} \tag{20}$$

2.2. Kurtz Powder Technique

The Kurtz powder technique[27] is a convenient method for screening large numbers of powdered materials for second-order nonlinear optical activity without needing to grow large single crystals. A laser is directed onto a powdered sample, and the emitted light is collected, filtered, and detected with a photomultiplier tube. The technique is crude in the sense that it detects a convolution of all the

tensor components of $\chi^{(2)}$ and makes little attempt to account for the propagation characteristics of the beams. Nevertheless, general trends can be observed and candidates for single-crystal studies identified.

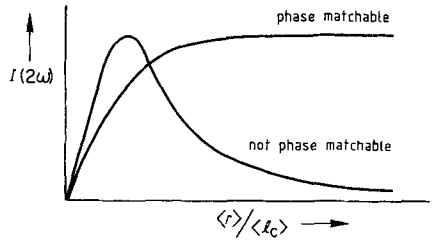


Fig. 7. Dependence of the second-harmonic intensity on the dimensionless quantity $\langle r\rangle/\langle l_c\rangle$, where $\langle r\rangle$ is the average particle size and $\langle l_c\rangle$ is the average coherence length according to the Kurtz powder method [27].

Figure 7 illustrates the application of this technique for phase-matchable and nonphase-matchable powders. Many crystals are birefringent; thus it is often possible to find a direction in a crystal in which a component of the nonlinear tensor $\chi^{(2)}_{ijk}$ will produce a harmonic wave that propagates with the same effective refractive index as the fundamental beam. This can be seen more easily in Figure 8 (top), where the refractive index for a uniaxial crystal is an ellipse. A light wave propagating through the crystal in a direction s has allowed polarization components at the major and minor axes of the ellipse perpendicular to s. One of these components η_0 (ordinary component of the refractive index) is independent of the direction of s, and the other depends on the angle θ between s and the y axis. A similar ellipse with different dimensions could be drawn at 2ω. If the two ellipses intersect, the possibility of a phase-matched tensor component exists. The lower plot indicates that an angle θ_p exists for phase matching.

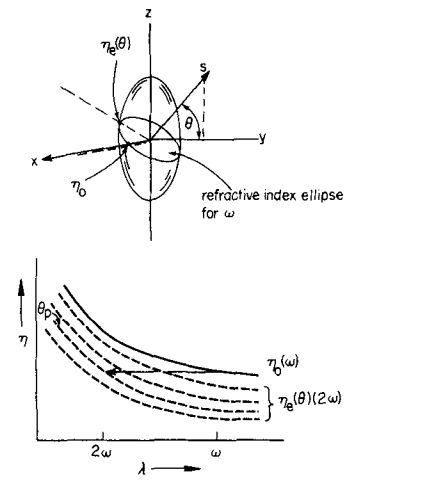


Fig. 8. Top: Refractive index ellipsoid for a uniaxial medium. s indicates the direction of an incident beam of light, and the semimajor and semiminor axes of the ellipse formed by the plane perpendicular to s with the refractive index ellipsoid define the allowed polarization directions for the propagating polarization. The refractive indices corresponding to those directions are the η_0 (ordinary) and $\eta_e(\theta)$ (extraordinary) components. The value of $\eta_e(\theta)$ depends on the angle between s and the x-y plane.—Bottom: If a direction in the medium can be found where $\eta_o(\omega)=\eta_e(\theta)_{2\omega}$, one type of phase matching is possible and large conversion efficiencies can be expected; θ_p is the phase-match angle.

It is possible to tell if a crystalline powder is phase matchable from a study of $I(2\omega)$ versus particle size (Fig. 7). Since phase-matched second harmonic generation is extremely efficient, the random particles which fortuitously sit at the phase-match angle provide most of the signal when the normal coherence length for nonphase-matched harmonic generation is exceeded. Great care must be used in applying this technique quantitatively, since the results are particle-size dependent.

3. Second-Order Nonlinear Optical Properties

As was indicated earlier, in the design of materials with large second-order nonlinear optical coefficients and other useful properties, the molecular hyperpolarizability must be optimized and then oriented in a medium (polymer, liquid, crystal) so that the propagating field can be transmitted from the medium. The electronic contributions to β and various approaches for obtaining the required noncentrosymmetry in the medium are discussed in this section.

3.1. Molecular Hyperpolarizability

Molecules containing conjugated π electronic systems with charge asymmetry exhibit extremely large values of β. The largest values are obtained when the molecule contains substituents that lead to low-lying charge-transfer resonance states (Fig. 9). The polarization can be visualized

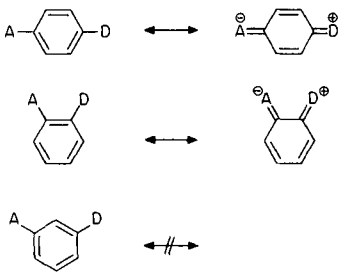


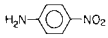
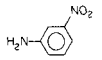
Fig. 9. Ground-state and lowest energy polar resonance forms for *p*- and *o*-substitution. Resonance is forbidden in the case of *m*-substitution.

as arising from contributions of the substituent-induced asymmetry of the π cloud and the σ skeleton of the molecule, as well as from field-induced mixing of the excited state (polar character) into the ground electronic configuration. The contributions to β have been separated into two parts for nitroanilines[28,29] [Eq. (21)].

$$\beta=\beta_{add}+\beta_{CT} \tag{21}$$

β_{add} is an additive part due to substituent-induced asymmetry in the charge distribution and β_{CT} is the charge-transfer term. Table 2 lists experimentally determined values of β for various nitroanilines and the monosubstituted parent compounds[29]. Also listed are values for β_{add}, obtained by simple vector addition of the experimentally determined values of β for nitrobenzene and aniline, and β_{CT}, obtained by a quantum mechanical calculation based on a charge-resonance two-level model described below. Note

Table 2. Experimental values of β for various nitroanilines as well as nitrobenzene and aniline. Also listed are the additive contribution β_{add} determined from summing the values for aniline and nitrobenzene and the charge-transfer contribution β_{CT} determined by the two-level model.

	$\beta_{exp} \times 10^{30}$ [esu]	β_{add}	β_{CT}
	34.5	3.4	19.6
	10.2	1.7	10.9
	6	3.3	4
	2.2	—	—
	1.1	—	—

the general agreement between the experimentally determined values for the disubstituted systems and the results of the calculations. Also note the obvious importance of the charge resonance structure, which, according to theory, should make its strongest contribution to β in the *p*-nitroaniline derivative.

In order to understand the origin of the additive term, it is useful to consider briefly the equivalent internal field model (EIF) for β in monosubstituted organic molecules[30]. In this model the charge asymmetry in the π system arises from the inductive effect of the substituent on the π system, leading to a "mesomeric" dipole moment $\Delta\mu$ in the aryl ring; $\Delta\mu$ is proportional to an internal field E_0 arising from the substituent [Eq. (22)].

$$\Delta\mu = \alpha E_0 + \gamma E_0^3 \simeq \alpha E_0 \tag{22}$$

Thus when an external field is applied, the total field is $E_T = E + E_0$, and Equation (2) becomes

$$P = \alpha E_T + \gamma E_T^3 \tag{23}$$

and by substitution

$$P = \alpha E_0 + \gamma E_0^3 + (\alpha + 3\gamma E_0^2) E + 3\gamma E_0 E^2 + \gamma E^3 \tag{24}$$

Chemical substitution on the ring therefore slightly modifies the linear polarizability (term 3), with appearance of a quadratic response (term 4). β, therefore, is given by the fourth term as

$$\beta = 3\gamma E_0 \tag{25}$$

and by substitution from Eq. (22)

$$\beta = \frac{6\gamma\Delta\mu}{\alpha} \tag{26}$$

Figure 10 shows a plot of experimentally determined values of β for a variety of monosubstituted benzenes versus the "mesomeric" dipole moment $\Delta\mu$[25]. Although there is

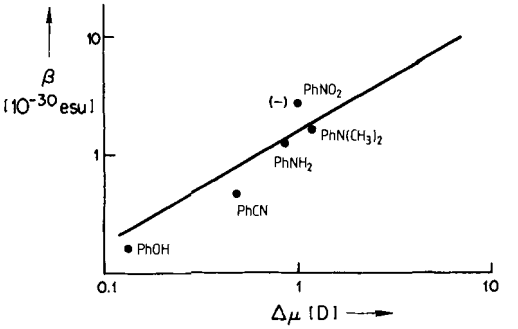


Fig. 10. Log/log plot of β versus the "mesomeric" dipole moment for some monosubstituted benzene derivatives [25].

some disagreement regarding the validity of the procedures for obtaining $\Delta\mu$[4], the agreement between experiment and theory is good and is supported by more-refined estimates of the induced dipole moment in the π system[31]. The certainty of the procedure for obtaining the additive components of β in Table 2 seems reasonable in view of the success of the EIF model for monosubstituted benzene derivatives. The vector-addition procedure assumes independent influences of the substituents.

The second term in Equation (21), β_{CT}, has been accounted for by various methods and degrees of sophistication ranging from Pariser-Parr-Pople calculations[25,32] to CNDO(S) studies with configuration interaction[33] and other SCF-LCAO methods[34], but a particularly useful approach for the physical organic chemist is the perturbation approach employing a two-level model[29]. In this model the β_{CT} term can be described in terms of a ground and first excited state having charge-transfer character (Fig. 9) and is related to the energy of the optical transition W, its oscillator strength f, and the difference between ground- and excited-state dipole moments $\Delta\mu_{g,e}$ by Equation (27).

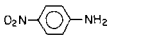
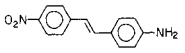
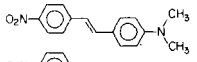
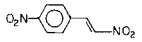
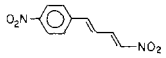
$$\beta_{CT} = \frac{3e^2\hbar^2}{2m} F(\omega) f \Delta\mu_{g,e} \tag{27}$$

$$F(\omega) = \frac{W}{[W - (2\hbar\omega)^2][W^2 - (\hbar\omega)^2]}$$

The term $F(\omega)$ accounts for dispersion and enhances β_{CT} as the fundamental frequency (ω) and harmonic (2ω) approach the energy of the charge-transfer function. Good agreement was obtained between the value of β_{CT} predicted by this expression and β_{exp} (assuming $\beta_{exp} = \beta_{CT}$) for a series of disubstituted benzene and stilbene derivatives[25] (Table 3).

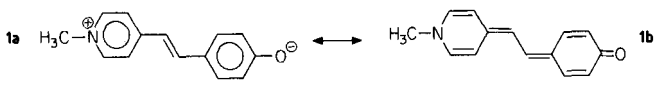
Morrell and *Albrecht*[33] tested the two-level model for *p*-nitroaniline by calculating β from CNDO(S)-determined electronic states using limited configuration interaction. They found that on using only the ground and first excited charge-transfer state, 75% of the value of β_{exp} could be accounted for. They obtained $\beta_{CT} = -25.1 \times 10^{-30}$ esu by this procedure. Inclusion of 60 excited configurations to more closely approximate the eigenstate associated with the first excited state gave $\beta = -34.3 \times 10^{-30}$ esu, which is in excellent agreement with β_{exp}. For the more extensively conjugated systems, the charge-transfer state is lower in energy with respect to other excited configurations, and we would

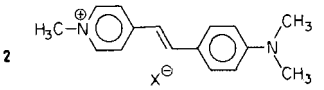
Table 3. Charge-transfer contribution β_{CT}, calculated from the two-level model, and experimental values β_{exp} for a series of benzene and stilbene derivatives.

	$\beta_{CT} \times 10^{30}$ [esu]	$\beta_{exp} \times 10^{30}$ [esu]
	19	34.5
	227	260
	383	450
	217	220
	715	650

expect the two-level scheme to agree even better with experimental data. The data in Table 3 appear to confirm this.

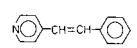
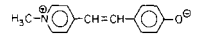
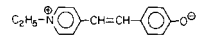
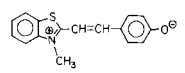
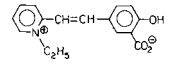
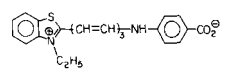
The success of the two-level model makes chromophore selection simple in many cases. If a molecule can be viewed as a superposition of resonating electronic structures with charge migration in the same direction along the molecular axis, β should be large. By this procedure, merocyanine dyes such as **1**[35] were shown to have the largest





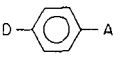
known molecular hyperpolarizability, and a noncentrosymmetric crystal containing the related dimethylaminostilbazolium chromophore **2**[5,36] was shown to have the largest known value of $\chi^{(2)}$ by the powder method. The product $\mu\beta$ was measured for a series of merocyanine-like compounds (Table 4). The importance of the charge resonance contribution is evident from the table. The reason for the low value of $\mu\beta$ for **6** (Table 4) is not clear, but the S atom may perturb the system in such a way that neither resonance form is predominant.

Table 4. Product of the dipole moment and β for molecules related to the merocyanine structure with the wavelength of the long wave absorption band λ_{CT}.

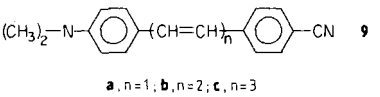
		$\mu\beta \times 10^{47}$ [esu]	λ_{CT} [nm]
	**3**	3.6	307
	**4**	760	570
	**5**	510	660
	**6**	50	560
	**7**	370	408
	**8**	150	498

Based on the theoretical notions described above, the effects of substituent patterns on a given chromophore are readily correlated with the electron donating and accepting strength of the substitution. Table 5 presents data on the effects of various substituents on β and λ_{CT}. Except for *p*-aminoacetophenone, the trends in λ_{CT} and β with the nature of the donor and acceptor are consistent with contribution of the charge-transfer state to β.

Table 5. Longest-wavelength absorption band and β for a series of *p*-disubstituted benzene derivatives.



A \ D	λ_{CT} [nm] (β [esu $\times 10^{30}$])			
	CH_3	OCH_3	NH_2	$N(CH_3)_2$
CN	232 (2.92)	247 (4.83)	269 (13.34)	297 (14.24)
CHO		(5.67)		352 (19.5)
$COCH_3$			310 (2.40)	
NO_2	280 (9.12)	314 (17.35)	378 (47.67)	418 (52.75)



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

Dulcic et al.[37,38] investigated the dependence of β on the length of the conjugated π-system for the compounds **9a**—**9c**; they found it obeyed an empirical law [Eq. (28)].

$$\mu_0\beta = Cn^k \tag{28}$$

$k \approx 2$, n = number of conjugated double bonds in **9**.

Although there appears to be a discrepancy in the sign of β, later experimental work reports the sign as being (−); the data in Table 3 therefore confirm this. The two-level model has generally been successful in accounting for the features of various classes of molecules, but caution should be ercercised when it is resorted to for predictions, since fortuitous combinations of ground- and excited-state electronic properties could exist where $\beta \approx 0$. This should be apparent, since β has not only a magnitude but also a sign.

3.2. Crystals and Polymers with Large $\chi^{(2)}$

From the regularities observed in β for various chromophore types, substituent patterns, and conjugation lengths, it is clear that a wide variety of molecular structures would exhibit extremely large second-order susceptibilities if they

could be incorporated into noncentrosymmetric structures. In this section various approaches to achieving this will be discussed.

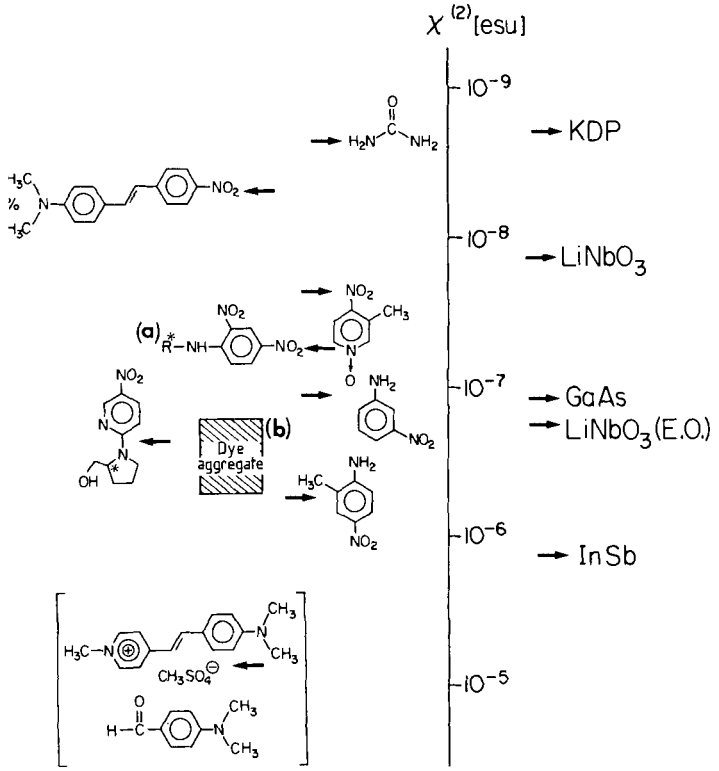


Fig. 11. $\chi^{(2)}$ scale for various inorganic crystals (right) and organic crystals and films (left). (a) R* = methoxycarbonylethyl. (b) Dye aggregate formed from an indolinobenzospiropyran and its ring-opened merocyanine form [39, 40]. *p*-Dimethylamino(nitro)stilbene was investigated in a poled liquid crystalline polymer. The arrows to the left and the right indicate the values of the substances.

Figure 11 depicts a $\chi^{(2)}$ scale with values of the susceptibility, generally obtained from second-harmonic-generation measurements for various organic and inorganic materials (for comparison). InSb has one of the largest known value of $\chi^{(2)}$, but, being a semiconductor, it is highly absorbing in the visible region of the spectrum and is therefore not useful for many applications. $LiNbO_3$ is the most extensively studied material for device applications involving the linear electro-optic effect. It suffers, however, from degradative photorefractive effects, which can cause history-dependent performance in various device applications. Potassium dihydrogen phosphate (KDP) has been used widely for phase-matched SHG of high-powdered near-IR lasers. In $LiNbO_3$, $\chi^{(2)}$(SHG) results from electronic polarization, whereas $\chi^{(2)}$(EO) results from polarization of the positions of the nuclei. In organic π electronic systems, $\chi^{(2)}$(SHG) and $\chi^{(2)}$(EO) both result from polarization of the π cloud, resulting in nearly identical values for the two effects. The measured values of $\chi^{(2)}(-2\omega;\omega,\omega)$[41] and $\chi^{(2)}(-\omega;\omega,0)$[42] for 2-methyl-4-nitroaniline (MNA), which are 540×10^{-12} and 500×10^{-12} esu, respectively, verify that the π electronic system is the primary contributor to both effects.

On the left side of Figure 11 are $\chi^{(2)}$ values for various organic materials. The nonlinear optical tensor components have been studied in detail for the five crystals indicated by the arrows closest to the scale. The principal $\chi^{(2)}$ tensor component was determined for *p*-dimethylaminonitrostilbene doped into a liquid-crystalline polymer, and the remaining materials were studied as powders.

Several points should be noted regarding Figure 11: Organic systems exhibit nonlinear coefficients which can exceed the best values for inorganic dielectrics and semiconductors. Furthermore, they are generally more useful because of increased transparency and resistance to laser damage. Although a number of crystalline organic materials have sufficiently large values of $\chi^{(2)}$ to be useful in integrated optics and for other applications, so far no polymer or other thin-film has been shown to have values of $\chi^{(2)}$(EO) approaching that of $LiNbO_3$. Considerable research on polymeric and non-polymeric organic materials remains to be done if technological utility is to be realized. Finally, the largest known value of $\chi^{(2)}$ (estimated by powder measurements) has been realized in an organic material.

The significance of the magnitude of $\chi^{(2)}$ immediately becomes apparent in equation (29), i.e. the equation for the efficiency of harmonic conversion by a plane wave propagating through a nonlinear material in the limit of low conversion[43].

$$\frac{I(2\omega)}{I(\omega)} = \Gamma^2 l^2 \,\mathrm{sinc}^2 \frac{\Delta k l}{2} \tag{29}$$

where

$$\Gamma^2 = \frac{(\chi^{(2)})^2 \omega^2 I(\omega)}{\eta^3 c^3 \varepsilon_0} \tag{30}$$

Here, l is the path length, ω is the fundamental frequency, η is the refractive index, c is the speed of light, ε_0 is the dielectric constant of a vacuum, and Δk (the phase mismatch) is $\omega/c\Delta\eta$. The sinc(x) function is defined as

$$\frac{\sin x}{x} = \mathrm{sinc}\, x \tag{31}$$

and sinc x approaches 1 as x approaches zero. Since the conversion efficiency is proportional to $(\chi^{(2)})^2$, a crystal of the type shown at the bottom of Figure 11 could be ca. 10^7 times more efficient than KDP or urea, which are normally used for megawatt lasers. A material of this type could provide large conversion efficiencies for solid-state diode lasers (≈ 10 mW power) if the appropriate nonlinear optical characteristics could be incorporated into the crystal. Thus, nonlinear optics could be extended to very low-power lasers. In designing technical devices many other advantages could be realized with coefficients in the 10^{-6} esu range. Another important consideration is brought out in Eq. (29): the implications for phase matching. At the phase-match condition $\Delta k = 0$ or $\eta_{2\omega} - \eta_\omega = 0$, $\mathrm{sinc}^2(x) = 1$, and the conversion efficiency is simply related to $\chi^{(2)} l^2$. (Other beam propagation characteristics, however, may lead to "walk off" or spatial divergence of the interacting fields, thus limiting the harmonic conversion.) If $\Delta k \neq 0$ the function oscillates as indicated previously. For Gaussian

beams and real crystals the situation is somewhat more complicated, but the same basic behavior, as illustrated by the plane-wave case, is followed.

In the following sections the properties of several of the materials in Figure 11 that illustrate key aspects or problems in second-order nonlinear materials will becommented on in more detail.

3.2.1. 2-Methyl-4-Nitroaniline (MNA)

The crystal growth and properties of MNA have been studied in detail by *Levine* et al.[41], who determined $\chi^{(2)}$ from harmonic generation studies, and by *Lipscomb* et al.[42], who measured the electro-optic coefficients. Earlier studies of β for *p*-nitroaniline[28] indicated that a noncentrosymmetric crystal containing the chromophore in an appropriate geometry could have very large $\chi^{(2)}$. It was hypothesized that a bulky substituent creating a sterically asymmetric ring could lead to the required crystal structure, and this was indeed verified by examination of a variety of monosubstituted *p*-nitroaniline derivatives. From powder measurements, MNA was identified as a candidate for single-crystal growth, and vapor transport and solvent growth techniques were used to obtain the crystals. The unit cell structure is illustrated in Figure 12. The Cc space group, which is contained in the m point group (monoclinic), has the unit cell symmetry elements indicated. Note that the polar axis P has a projection of the dipole moment onto the P axis determined by θ and ϕ.

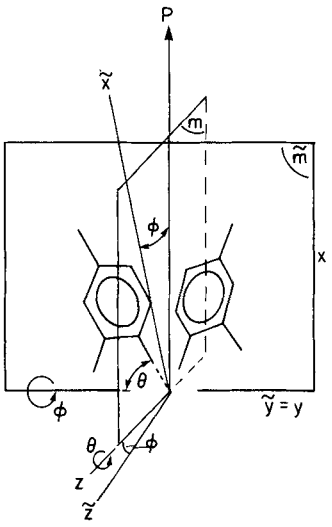


Fig. 12. View of the unit cell of 2-methyl-4-nitroaniline (MNA). The space group Cc is isomorphous with the C_s point group, which has a polar axis P and mirror plane m̃. θ and ϕ are 70 and 8°, respectively; x, y, z are the dielectric principal axes, m is a pseudo-mirror plane. The large projection of the molecular polar z axis onto P makes this an ideal candidate for electro-optic applications. Structural data from [12].

Oudar and *Zyss*[12] have analyzed the relationship between the various components of the hyperpolarizability tensor β_{ijk} and the macroscopic nonlinear coefficients $\chi^{(2)}_{ijk}$ for various crystal symmetries. Their objective was to determine the space groups that would give the largest achievable nonlinearities as well as the dependence of the various nonlinear coefficients on the geometry of the molecule in the unit cell. For MNA the coefficient $\chi^{(2)}_{zzz}$ should be maximized when the angle θ is 90°. This should be apparent, since for a small dihedral angle ϕ the projection of the polar charge-transfer axis will be maximum when it is parallel to the crystal polar axis. $\chi^{(2)}_{zzz}$ therefore gives a very large electro-optic coefficient[42], but since the polarization and field directions are colinear, this could not possibly be a phase-matchable coefficient for SHG. χ_{zyy}, on the other hand, is a phase-matchable coefficient and for this space group is a maximum for $\theta = 54°$, $\phi = 0$: *Oudar* and *Zyss*'s analysis[12] predicts an increase in $\chi^{(2)}$ by a factor of 3.5 and more than an order of magnitude greater conversion efficiency for optimum orientation of an MNA type molecule over that actually observed [41, 42]. Although the relationship between crystal structure and second-order nonlinear properties is complex, the details have been elucidated and summarized[12]. The maximum achievable value $\chi^{(2)}_{(max)}$ as a fraction of what one would predict from the oriented rigid gas model described earlier is given in Table 6.

Table 6. Polar point groups and maximum fractional value of the rigid oriented gas $\chi^{(2)}$ for a phase-matched interaction and for optimum molecular orientation in the unit cell.

Point group	$\chi^{(2)}_{(max)}$
1, 2, m, mm2	0.38
62M, 6, 3, 3M, 32	0.25
222, 6mm, 6, 4mm, 42M, 23, 43M	0.19
4	(no possible phase interaction)

3.2.2. trans-4'-Dimethylamino-N-Methylstilbazolium Methyl Sulfate (DSMS)

The title chromophore, DSMS **2**, $X = H_3COSO_3^{\ominus}$, was selected according to the principles outlined at the end of Section 3.1. It contains extremely electron-rich and electron-deficient groups linked in a *trans*-stilbene fashion, leading to an expanded conjugated π-system. The possibility of metastasis of the counterion suggests investigating a variety of steric and coulombic influences on the crystal structure of a common chromophore. SHG harmonic intensity measurements are shown in Table 7 for a variety of materials[5,36]. The caution with which data of this type must be viewed is illustrated by comparison of *m*-nitroanil-

Table 7. Harmonic intensity (relative to *m*-nitroaniline) determined by the Kurtz powder method.

Crystalline powder	Relative harmonic intensity
α-Quarz	0.008
m-Nitroaniline	1
MNA	3
$1^{\oplus}$(+)-Campher sulfonate$^{\ominus}$	0.007
$2^{\oplus}$ $I^{\ominus}$	0
$2^{\oplus}$ $IO_3^{\ominus}$	0.01
$2^{\oplus}$ $NO_3^{\ominus}$	0.5
$2^{\oplus}$ $C_6H_5CH{=}CHCO_2^{\ominus}$	1.5
$2^{\oplus}$ $ClO_4^{\ominus}$	5
$2^{\oplus}$ $BF_4^{\ominus}$	10
$2^{\oplus}$ $ReO_4^{\ominus}$	18
$2^{\oplus}$ $CH_3OSO_3^{\ominus}$	30

ine and MNA. Their coefficients $\chi^{(2)}$ differ by a factor of about 3, yet their harmonic intensities differ by a factor of only about 3 rather and not—as we might expect from Equation (29)—by a factor of 9. Since no attempt was made to classify particle sizes, and the powder technique is known to be very dependent on this and other factors, variances of this sort might be expected. Nevertheless, the DSMS powder showed an order of magnitude higher conversion efficiency than MNA, which has the largest known $\chi^{(2)}$ value reported to date for a crystal. This constituted justification for growing DSMS single crystals and characterizing the linear and nonlinear properties of the crystal. Preliminary crystal structure studies have shown that the crystal is described in the mm2 point group, for which a large value of $\chi^{(2)}$ is expected (Table 6). Furthermore, the molecular dipolar axis is tilted at an angle of 34° with respect to the twofold screw (polar) c axis. Since a tilt axis of 54° 74′ would be optimum for phase-matched SHG and 0° for the linear electro-optic coefficient[11], the crystal structure is a compromise and is expected to give large values for both effects.

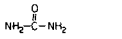
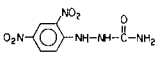
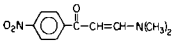
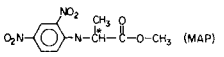
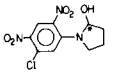
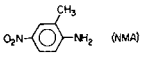
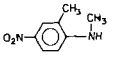
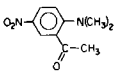
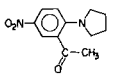
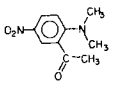
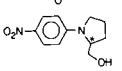
3.2.3. Materials Optimized for SHG with Semiconductor Lasers

Twieg and *Jain*[44] exhaustively studied molecules containing the nitroaniline and related chromophores for SHG activity by the powder technique. Their objective was to identify powders with large SHG conversions and transparency suitable for use with 0.80—1.5 μm lasers. Table 8 lists harmonic efficiency measurements for powders of various classes of substances. Generally, only the compound showing the largest efficiency for a particular class is shown. For instance, **10** is a substituted urea derivative, **11** a push-pull alkene, **13** a MAP analogue, etc. Given the uncertainties of the powder technique as applied here, any of these compounds would be reasonable candidates for further study, depending on factors such as the ease of crystal growth, oxidative stability, toxicity, etc. Compound **19** is particularly interesting because its powder efficiency is about half that of the stilbazolium salt mentioned previously, yet it is very transparent in the visible region owing to the blue shift attributed to the nitrogen heteroatom (cut off ≈430 nm).

3.2.4. Molecularly Doped and Aligned Polymers

A possible route to preparing polymeric films with large second-order nonlinear coefficients is to remove the orientational averaging of a dopant molecule with large β by application of an external DC electric field to a softened film. This might be accomplished by heating the film above the host polymer glass-transition temperature T_g, then cooling the film below T_g in the presence of the external field. The poling would provide the alignment predicted by the Boltzmann distribution law and impart $C_{\infty v}$ symmetry to the film. Such a process is illustrated schematically in Figure 13. For this particular symmetry group[45] there are two nonvanishing coefficients, $\chi^{(2)}_{zzz}$ and $\chi^{(2)}_{zxx}$, i.e. incident beam polarized parallel (zz) and perpendicular

Table 8. Harmonic intensity (relative to that of urea) for a series of powders. The numbers in parentheses are relative to *m*-nitroaniline and are obtained by comparing the MNA values in Tables 7 and 8 and applying the appropriate multiplier to the values in Table 8.

Crystalline powder		Rel. harmonic intensity
		1.0 (0.13)
	**10**	8.8 (1.20)
	**11**	7.5 (1.02)
	**12**	10.0 (1.36)
	**13**	32.0 (4.36)
	**14**	22.0 (3.0)
	**15**	80.0 (10.9)
	**16**	115.0 (15.6)
	**17**	80.0 (10.9)
	**18**	70.0 (9.55)
	**19**	160.0 (21.8)

(xx) to the z polar axis. A film with these properties would have an electro-optic coefficient proportional to $\chi^{(2)}_{zzz}$, and phase matching for SHG could be achieved through the smaller $\chi^{(2)}_{zxx}$ [46]. Alternatively, harmonic generation could be achieved by wave guiding, which would impart additional flexibility in phase matching. The advantages of wave-guided SHG[47] will not be discussed here, but a tremendous potential advantage of polymer films over crystals lies in the fabrication of thin films for wave-guided nonlinear optical devices.

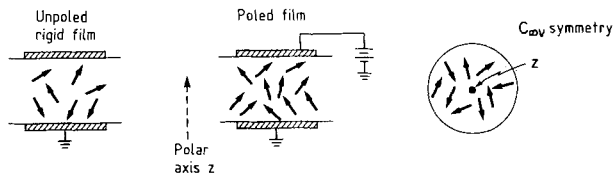


Fig. 13. Schematic of imparting $C_{\infty v}$ symmetry (polar axis, isotropic perpendicular to the polar axis) to an isotropic medium containing permanent dipoles with an external electric field E.

To predict the value of $\chi^{(2)}$ after poling, one needs to evaluate the expressions (32) and (33).

$$\chi^{(2)}_{zzz} = NF\beta_{zzz}\langle\cos^3\theta\rangle \tag{32}$$

$$\chi^{(2)}_{zxx} = NF\beta_{zzz}\langle(\cos\theta)(\sin^2\theta)(\cos\phi)\rangle \tag{33}$$

These expressions resemble that for the oriented rigid gas [Eq. (7)], where F is the total local field-factor correction, θ is the angle between the molecular polar z axis and the laboratory (field-induced) z axis, and ϕ is the projection of the molecular z axis onto the laboratory x axis. Since these projections are induced by an external field, which competes with thermal randomizing effects, the Boltzmann thermal averages of these projections must be computed [Eqs. (34) and (35)][46].

$$\langle\cos^2\theta\rangle = \mu \cdot E/5kT \tag{34}$$

$$\langle(\cos\theta)(\sin^2\theta)(\cos\phi)\rangle = \mu \cdot E/15kT \tag{35}$$

μ is the dipole moment of the dopant molecule and E is the applied DC field. The $\langle(\cos\phi)\rangle$ is isotropic, since no polar alignment is induced orthogonal to the field direction.

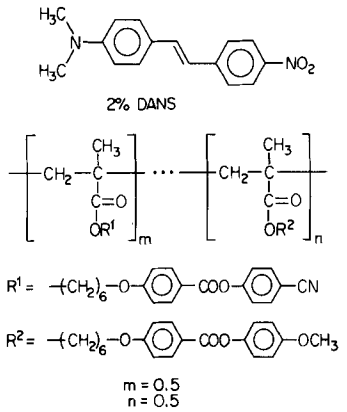


Fig. 14. Components of a molecularly doped liquid-crystalline polymer film oriented by an external field and which exhibited large SHG [46].

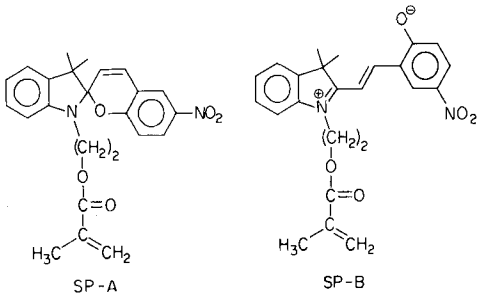
The principles outlined above were used to induce a second-order nonlinearity in *p,p'*-dimethylaminonitrostilbene (DANS) doped at 2 wt% into a liquid-crystalline polymer host (Fig. 14). The host polymer belongs to a class of polymers in which mesogenic chromophores are attached via a flexible $(CH_2)_n$-spacer to the rigid backbone[48]. It was shown that polymers of this general structure, which exhibit a nematic mesophase above T_g, could be aligned by an external field, eliminating the light-scattering nematic texture, and that the alignment was retained upon cooling below T_g. DANS, for which $\beta = 4.5 \times 10^{-28}$ esu[49], showed a pleochroic effect in the polymer host; the molecular z axis tended to align with the long axis of the mesogens, causing it to exhibit linear dichroism in its absorption band. Under these circumstances the electric-field-induced *polar* alignment, as opposed to the *axial* alignment associated with pleochroism, requires the thermal averages discussed above. If Ising model statistics are assumed to describe polar alignment in an axial environment, Equation (32) must be multiplied by a factor of 5. Equation (36) then holds.

$$\chi^{(2)}_{zzz}(\text{Ising}) = NF\beta_{zzz}\mu \cdot E/kT \tag{36}$$

$\chi^{(2)}_{zzz}$ was measured as 6×10^{-9} esu for an alignment field of 0.6 V/μm, while $\chi^{(2)}_{zzz}$(Ising) was calculated to be 3×10^{-9} esu. This is remarkable and perhaps coincidentally good agreement in view of the approximations made in the calculations and the experimental complications. Nevertheless, the experiments demonstrate that electric-field-induced alignments that can be retained in the film upon removal of the field can give rise to large second-order nonlinear coefficients.

3.2.6. Field-Induced Alignment of Quasicrystalline Dye Aggregates

A final example of a noncrystalline but highly ordered system where SHG can be induced by an external field is provided by "quasicrystals" obtained from the photolysis of indolinobenzospiropyrans in nonpolar solvents in the presence of an external field[50]. Upon irradiation, the spiro form (SP-A) undergoes a sequence of photochemical steps[51] leading to the formation of complexes A_nB, which in turn form polar aggregates. The insoluble aggregates



can be isolated between the electrodes used to apply the fields and show threadlike morphologies along the field lines. In SHG studies on threads formed in the presence and absence of external fields[39], the following observations were made:

1. Threads formed in the absence of a field exhibit no SHG.
2. SHG could be induced in these samples when DC external fields were applied.
3. Threads formed in the presence of electric fields exhibit strong SHG when measured with radiation polarized parallel to the threads, but the SHG was considerably weakened with light perpendicular to the threads. In each case these measurements were carried out with the field removed.
4. A larger SHG response was detected when a secondary field was applied parallel to the threads.

The details of these observations led to the proposal of a model consisting of stacks (Fig. 15) of near-neighbor interacting dipoles described by the following parameters: θ is the angle made by the dipoles with respect to the stack axis, r is the distance between dipoles, $U(\uparrow\downarrow)$ and $U(\uparrow\uparrow)$ are the interaction energies between antiparallel and parallel neighbors, respectively, and $U(\uparrow)$ and $U(\downarrow)$ are the dipolar interaction energies in the direction of and against the field, respectively. The model predicts that for $\theta < 54°44'$ the parallel configuration will dominate. The spectral red shift of the aggregates is consistent with the parallel coupling of the induced dipoles[50]; if they are almost parallel

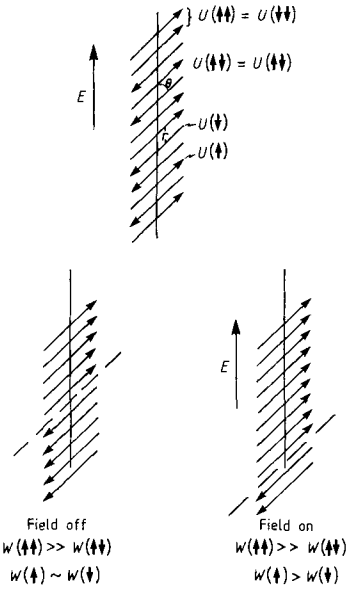


Fig. 15. Top: Parameters for a stack of molecular dipoles separated by r and making an angle θ with respect to the stack axis. Only the near-neighbor interaction energies $U(\uparrow\uparrow)=U(\downarrow\downarrow)$ and $U(\uparrow\downarrow)=U(\downarrow\uparrow)$ and dipolar energies against ($U(\downarrow)$) and in ($U(\uparrow)$) the direction of the applied field are considered. Bottom: For $\theta<54°44'$, long sequences of parallel dipoles are favored. A field increases the relative number of dipoles in the direction of the field (W denotes the appropriate probability distribution [39]).

to the permanent molecular dipoles, the red shift is a strong indicator of a parallel arrangement of molecular dipoles. The model uses the classical partition function to calculate the probability distributions $W(\uparrow\uparrow)$, $W(\downarrow\uparrow)$, $W(\uparrow)$, $W(\downarrow)$. For aggregates formed in the absence of a field and with $\theta<54°44'$, randomly oriented aggregates consisting of arrays of parallel dipoles with occasional changes in phase would be expected. This is consistent with the lack of SHG observed for samples formed in the absence of a field. When a field is subsequently applied, a signal with a quadratic field dependence due to movement of the phase boundary is expected and indeed observed. For aggregates formed in the presence of a field we would expect not only a much larger signal, owing to preferential orientation of the aggregates as they are formed, but also a quadratic field-dependent signal; these features are in fact observed. The overall agreement between experiment and theory is gratifying for such a complex system. Owing to the particulate nature and size of the aggregates, however, it was not possible to extract a value for $\chi^{(2)}$ for this system.

4. Outlook

Although considerable progress has been made, both in understanding the electronic origins of molecular nonlinearities in organic π systems, as well as in our ability to explain quantitatively the relationship of molecular arrangements in a crystal or polymer to the observed nonlinearities a posteriori, the design and fabrication of new systems with optimized nonlinear optical properties, linear optical properties, and adjunct properties remains a major challenge for chemical research. The major areas of solid-state chemical research that will affect this field are crystal design and growth, crystal thin-film technology, and polymer thin-film technology.

The design of crystalline materials that lend themselves to the growth of high-quality, large single crystals at a reasonable cost is a major challenge. Since the categories of application for such materials span a wide variety of requirements in terms of device design (frequency doublers, frequency mixers, parametric oscillators, etc.), available laser power, transparency, and cost, no attempt will be made to enumerate a specific set of requirements as a target for future research. One special case worth mentioning, however, is the use of urea crystals to extend the range of usability of dye lasers to 240 nm and double the output of the popular blue/green argon ion laser at 480 nm via SHG[52]. Due to its phase-matching characteristics, urea exhibits high SHG efficiency relative to the popular inorganic crystals; furthermore, it has a high nonlinear coefficient, and it is possible to grow large high-quality crystals that have high damage threshold and can be cleaved and polished. These characteristics have spawned commercial development efforts for nonlinear crystals of urea. In contrast, dimethylurea crystals[53], although they extend the phase-matching range even further into the UV and have other desirable optical properties, nevertheless have poor mechanical properties, which make them unsuitable for manufacturing.

In addition to the applicability of single-crystal technologies, a variety of opportunities exist for thin-film structures where planar processing techniques might permit deposition onto Si or other substrates. Large $\chi^{(2)}$ or $\chi^{(3)}$ values might permit the fabrication of the active components for optical circuitry, making use of the nonlinear refractive index of such materials. Three promising approaches have emerged for obtaining the required asymmetry for large $\chi^{(2)}$: 1) Molecularly doped polymers with electric field alignment, 2) topochemical polymerization of asymmetric diacetylene monomers[54], and 3) Langmuir-Blodgett multilayer techniques[54]. The first approach offers considerable flexibility in terms of design and selection of materials, but requires that permanent alignment be imparted by application of an external electric field. The second approach is still beset with problems regarding single-crystal growth and the restrictions of the highly conjugated polymerized diacetylene chain. Langmuir-Blodgett techniques may offer the ultimate in chemical design flexibility but require extensive resources and expertise.

Many of the electro-optic functions occurring through $\chi^{(2)}$ could also be achieved through the quadratic electro-optic effect if materials with sufficiently large $\chi^{(3)}$ could be developed without the stringent symmetry requirements of the linear electro-optic materials. Thin films containing the polydiacetylene chain formed by Langmuir-Blodgett techniques have one of the largest known values of $\chi^{(3)}$[55] ($\sim 10^{-11}$ esu), which may be useful for certain applications. An additional advantage of Langmuir-Blodgett films is that radiation-induced polymerization leads to a convenient method of patterning that might be used for device fabrication.

Although considerable progress has been made in this multidisciplinary field over the past several years, much creative chemistry still remains to be done if broad tech-

nological utility of organic/polymeric, nonlinear optical materials is to be brought to fruition.

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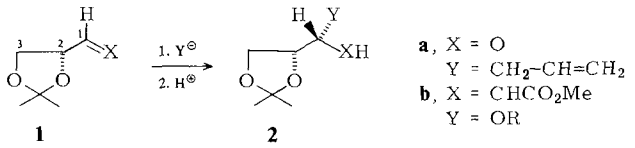
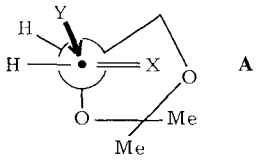
Optional Diastereo- and Enantioselective Synthesis of Vicinal *threo*- or *erythro*-Dihydroxy Derivatives**

By *Johann Mulzer**, *Michael Kappert*, *Gottfried Huttner*, and *Ibrahim Jibril*

Diastereo- and enantioselective synthesis of compounds having the 1,2-di-*O*-structural element (such as **2**) are gaining increasingly in importance[1]. Our general method for the preparation of compounds of this structure type exploits the finding that the isopropylidenediol moiety in **1** induces *ul*-selective nucleophilic attacks at the neighboring prochiral C-1 via transition state **A**[2]. Depending on the sequence in which the residues X and Y are introduced, adduct **2** is obtained in either *threo*- or *erythro*-configuration[2]. Since **1** is available in either (*R*)- or (*S*)-configuration[3], all four stereoisomers of **2** can be prepared.

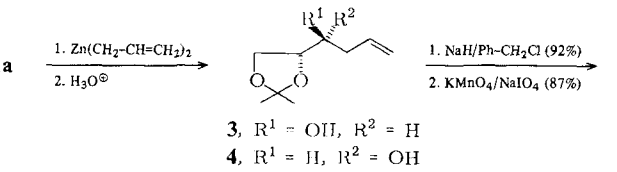


1 **2**

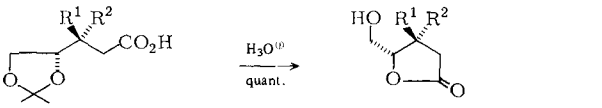


A

Diallylzinc reacts *erythro*-selectively with the aldehyde **1a** to afford **3**, which together with the minor isomer **4** (**3** : **4** = 9 : 1) is converted via the 3-benzyloxycarboxylic acids **5/6** into the γ-lactones **7c/8c**. The isomers are separated by column chromatography (SiO_2, pentane/ether 4 : 1) either via the methyl ester of **5/6** or at the stage of the lactones **7c/8c**. The configuration of the adducts **3/4** and, hence, that of all the subsequent products, has previously been determined unequivocally by correlation with known compounds[4].



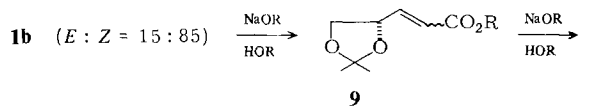
3, R^1 = OH, R^2 = H
4, R^1 = H, R^2 = OH



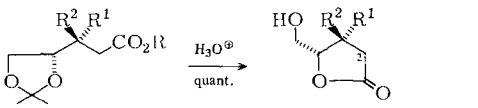
5, R^1 = OCH_2Ph, R^2 = H
6, R^1 = H, R^2 = OCH_2Ph

7c, R^1 = OCH_2Ph, R^2 = H
8c, R^1 = H, R^2 = OCH_2Ph

The second route makes avail of the *threo*-selective addition of sodium alkoxides to the acrylic esters **1b** (Table 1), readily accessible from **1a**[5], which leads to the Michael adducts **10/11**. Separation of **10/11** by column chromatography and "recyclization" affords **7** and **8**, respectively;



9



10, R^1 = OR, R^2 = H
11, R^1 = H, R^2 = OR

8, R^1 = OR, R^2 = H
7, R^1 = H, R^2 = OR

7-11: **a**, R = Me, **b**, R = Et; **c**, R = CH_2Ph

Table 1. Diastereomers **10/11** (**8/7**) formed in the addition of 1 mol equiv. NaOR to **9** (3 M in HOR). Total yields of **10** and **11** > 85%.

No.	R	*T* [°C]	*t* [min]	Products	Ratio [a] **10** : **11**
1	Me	25	6	**10a/11a**	60 : 40
2	Me	0	6	**10a/11a**	75 : 25
3	Me	−20	6	**10a/11a**	85 : 15
4	Me	−50	6	**10a/11a**	91 : 9
5	Me	−78	60	**10a/11a**	95 : 5
6	Et	0	6	**10b/11b**	63 : 37
7	Et	−50	60	**10b/11b**	86 : 14
8	CH_2Ph	−10	120	**10c/11c**	76 : 24
9	CH_2Ph	−50	[b]	[b]	[b]

[a] Determined by ^{1}H-NMR for **10a/11a** (OMe singlet at δ = 3.45 (**10a**) and 3.42 (**11a**), respectively, in $CDCl_3$, TMS) and by ^{13}C-NMR for **10b/11b** and **10c/11c** (C-2 signals (80 MHz, $CDCl_3$, TMS)) at $\delta \approx 36.10$ (**10b**), 37.52 (**11b**), 35.98 (**10c**), 37.31 (**11c**). [b] Solution solidifies at ca. −20°C; no reaction.

derivatives **7c** and **8c** are identical with the compounds obtained by the first route[6]. In addition, a crystal structure analysis is available for **8a**[7].

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Alkoxide addition to the double bond[8,9] of **1b** in the synthesis of **7b** and **7c** is preceded by rapid transesterification to **9b** and **9c**, respectively, which is >95% complete before appreciable amounts of **10/11** are formed. The product ratio **10/11** depends in the first instance on the reaction temperature; appreciable selectivities occur below −50°C. Complete conversion can only be achieved if the alkoxide is added in equimolar amounts. The reaction rate decreases along the sequence $^{\ominus}$OMe, $^{\ominus}$OEt, $^{\ominus}OCH_2Ph$: Only $^{\ominus}$OMe still adds completely to **1b** at −78°C; for $^{\ominus}$OEt this occurs only down to −50°C (Table 1, No. 7), and $^{\ominus}OCH_2Ph$ does not react with **1b** below −20°C. At the same temperature (Nos. 2, 6, 8), the differences in selectivity are small. The reaction proceeds under conditions of kinetic control; at room temperature, **10a/11a** undergo only transesterification with sodium benzylate, and no exchange of the 3-OMe occurs. The same is true for **10c/11c** and sodium methoxide.

The central diol unit in **2a** and **2b** is ideally suited for transformation into natural-product derivatives since the hydroxy groups can be differentiated easily. The terminal functional groups CH_2–O, CH_2=CH_2, and CO_2Me may be used for chain extension on both sides. The OMe-protecting group in **10a** can be removed at a later stage of the reaction[10].

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[6] Correct elemental analyses were obtained for all compounds. Further data for **7c**, **8a**, and **8c**: **7c**: m.p. = 65–66°C, $[\alpha]_D^{20}$ 38.6 ($CHCl_3$, c=4); ^{1}H-NMR ($CDCl_3$, 60 MHz, TMS): δ=2.48 (dd, J=18 and 3 Hz, 3-H), 2.86 (dd, J=18 and 7 Hz, 3-H), 3.37–4.0 (m, 5-H), 4.15–4.33 (m, 4-H), 4.47 (s, OCH_2Bn), 4.57 (br, OH), 7.25 (s, Ph).—**8a**: m.p. = 89–90°C, $[\alpha]_D^{20}$ −33.1 ($CHCl_3$, c=2), ^{1}H-NMR ($CDCl_3$): δ=2.70 (d, J=5 Hz, 3-H), 3.07 (br, OH), 3.35 (s, OMe), 3.95 (d, J=5 Hz, CH_2OH), 4.25 and 4.62 (respectively, q, J=5 Hz, 4- and 5 H).—**8c**: oil, $[\alpha]_D^{20}$ −13° ($CHCl_3$, c=2); ^{1}H-NMR : δ=2.65 (d, J=5 Hz, 3-H), 3.3 (br, OH), 3.85–4.02 (m, CH_2OH), 4.17–4.70 (m, OCH_2Ph+4-H, 5 H), 7.25 (m, Ph).

[7] Structural data: $C_6H_{10}O_4$ (146.15), m.p. = 89–90°C, orthorhombic, $P2_12_12_1$, a=4.469(2), b=7.529(4), c=20.93(1) Å, V=704 Å^3, Z=4, ρ_{calc}=1.38 g cm^{-3}, $Mo_{K\alpha}$-irradiation (graphite monochromator), λ=0.71069 Å, 2° < θ < 42°, 481 observed reflections, 447 of which with $I > 2\sigma$, R=5.34, R_w=5.66. ω-Scan with 1.8 < $\dot{\omega}$ < 29.3° min^{-1}. Further details of the crystal structure investigation can be obtained from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, by quoting the depository number CSD 50934, the names of the authors, and the journal citation.

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[10] T. Greene: *Protective Groups in Organic Synthesis*, Wiley, New York 1981, p. 15.

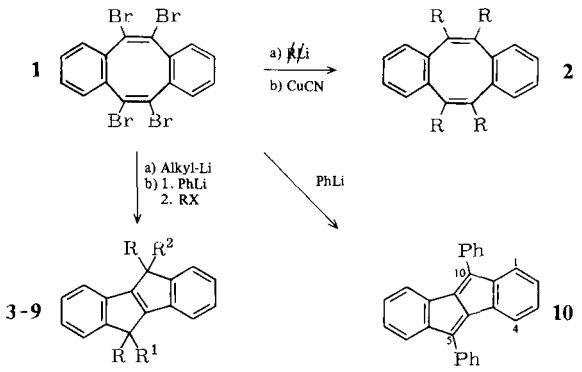
Carbanion-Induced Skeletal Rearrangements: From the Dibenzo[*a,e*]cyclooctene to the Indeno[2,1-*a*]indene Framework**

By *Dieter Hellwinkel**, *Hans-Joachim Hasselbach*, and *Frank Lämmerzahl*

In our studies of peripherally bridged tetraphenylene derivatives[1], we have explored methods of introducing substituents suitable for further annellations[3] by nucleophilic substitution of the bromine atoms of 5,6,11,12-tetrabromodibenzo[*a,e*]cyclooctene **1**[2].

If **1** is allowed to react with excess organolithium compounds in tetrahydrofuran between −78°C and room temperature, not the tetraorganobenzo[*a,e*]cyclooctenes **2**, products of a simple addition-elimination mechanism[4,5], but only isomers with the indeno[2,1-*a*]indene framework are obtained. In this way, methyl- and *n*-butyllithium afford up to 70% of the 5,5,10,10-tetraalkyl-5,10-dihydroindeno[2,1-*a*]indenes **3**, **4**, whereas with *tert*-butyllithium mixtures of the tri- and di-*tert*-butyl derivatives **5**, **6** and, with a large excess of *t*BuLi, moderate yields of the tri-*tert*-butyl derivative **5** are obtained. In contrast, with phenyllithium the red-brown 5,10-diphenylindeno[2,1-*a*]indene **10** is obtained, which is identical with a reference compound synthesized using an independent procedure[6] [m.p. = 247–248°C, ^{1}H-NMR ($CDCl_3$): δ=6.84 (td, 2H), 6.90 (td, 2H), 7.03 (dm, 2H), 7.24 (dm, 2H), 7.45 (tt, 2H), 7.52 (tm, 4H), 7.67 (dm, 4H)].

Treatment of the phenyllithium reaction mixtures, which like the others are deeply colored, with ethanolic hydrogen chloride, iodomethane, or iodobenzene at low temperatures affords the derivatives **7**–**9** of 5,10-dihydroindeno[2,1-*a*]indene.



	R	R¹	R²	m.p. [°C]
3	Me	Me	Me	214
4	*n*Bu	*n*Bu	*n*Bu	154
5	*t*Bu	*t*Bu	H	145
6	*t*Bu	H	H	165
7	Ph	H	H	286
8	Ph	Me	Me	276
9	Ph	Ph	Ph	351

The structures of **3** to **9** were corroborated by elemental analysis, and, in particular, by the ^{13}C-NMR spectra, whose characteristic signals are summarized in Table 1.

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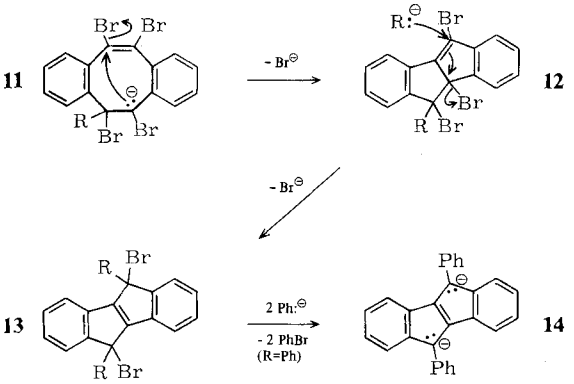
Table 1. Selected ^{13}C-NMR data for **3**-**9** ($CDCl_3$, rel. TMS, δ-values) [a].

Position	3	4	5	6	7	8 [b]	9
5, 10	44.9	54.0	68.6/ 55.1	56.3	49.9	52.4/ 52.3	61.8
4a, 9a	137.9	140.7	143.2/141.7	142.8	138.2	142.4/142.3	141.4
4b, 9b	155.5	155.3	159.0/154.6/	155.4	152.5	159.2/157.9/	155.9
5a, 10a	158.9	155.9	154.2/151.4	150.9	151.2	156.8	154.0

[a] ^{1}H-NMR ($CDCl_3$, δ-values): **3**: 1.53 (s, 12H), 7.22 (td, 2H), 7.29 (td, 2H), 7.40 (d, 2H), 7.42 (d, 2H); **4**: 0.65 (t, 12H), 0.71—1.3 (m, 16H), 2.00 (t, 8H), 7.1—7.4 (m, 8H); **5**: 1.03, 1.08 (each s, together 18H), 1.28 (s, 9H), 3.59 (s, 1H), 7.00—7.90 (m, 8H); **6**: 1.18 (s, 18H), 3.46 (s, 2H), 7.06 (td, 2H), 7.22 (td, 2H), 7.42 (d, 2H), 7.48 (d, 2H); **7**: 4.97 (s, 2H), 7.05—7.20 (m, 6H), 7.20—7.35 (m, 12H); **8** [b]: 1.94, 1.99 (each s, together 6H), 7.0—7.5 (m, 18H). [b] As a *cis/trans*-mixture which melts at 240°C.

A preliminary reaction scheme which accounts for all the products isolated involves initial addition of an $R^{\ominus}$ ion to **1** to yield **11**, which subsequently undergoes transannular addition-elimination to give **12**[7]. Compound **12** could then react with additional $R^{\ominus}$ to afford intermediate **13**, which can react in various ways: with alkyllithium, further substitution occurs to furnish the tetra-, tri-, and dialkyl derivatives **3**—**6**. Phenyllithium can either attack a bromine atom to form, via elimination, **10**, or can undergo a double halogen-metal exchange affording the dianion **14**[8], which can be trapped with electrophiles to give **7**-**9**.



In only one instance have we observed nucleophilic substitution at **1** with retention of the skeleton: reaction of **1** with copper(I) cyanide in *N*-methylpyrrolidone gives rise to 30% 5,6,11,12-dibenzo[*a*,*e*]cyclooctenetetracarbonitrile **2** (R = CN) [m.p. = 350°C, ν_{CN} = 2210 cm^{-1}], whose symmetrical ^{1}H-NMR signal pattern ($\delta_{AA'}$ = 7.59, $\delta_{BB'}$ = 7.48) substantiates that the framework has not undergone rearrangement.

In the meantime, we have obtained evidence which indicates that reactions of **6** with less polar Grignard compounds and organolithium compounds in less polar solvents such as diethyl ether also proceed with retention of the skeleton.

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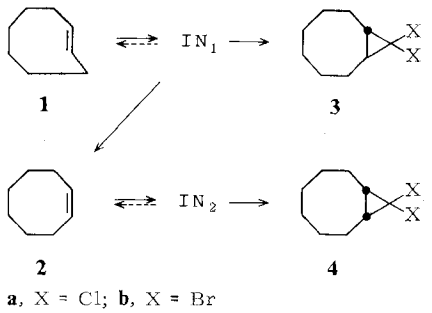
Stereochemical Evidence Supporting the Intermediate Mechanism of Dihalocarbene Addition**

By *Eckehard V. Dehmlow** and *Roland Kramer*

Singlet halocarbenes generally react with alkenes via *cis*-addition, which is often envisaged as a concerted (one-step) process. More recent kinetic data on the additions of CCl_2, CBr_2, and C_6H_5Cl have nevertheless been interpreted in terms of reversible, intermediate formation of a charge-transfer complex[1-3]. These results corroborate the two-step mechanism proposed by *Skell* et al. for CX_2 as early as 1956[4]. Products which demand a mechanism involving an intermediate arise, to the best of our knowledge, in halocarbene reactions[5] in only three cases[6-8]. In particular, for the reaction of *trans*-cyclooctene **1** with CBr_2 both the stereospecific formation of **3b**[9] and the formation of a large amount of **3b** in addition to a little **4b**[8] were reported in 1970. According to [8], partial isomerization **1** → **2** occurs under the reaction conditions.

With the aid of 300 MHz ^{1}H-NMR spectroscopy it is easy today to test the purity of *trans*- and *cis*-cyclooctene **1** and **2**[10], respectively, as well as of adducts **3a**, **b** and **4a**, **b**[11]. Mixtures of **3** and **4** can also be analyzed using capillary gas chromatography[12]. We found that after 10 min (±)-**1** has reacted completely and stereospecifically with CCl_2 generated by phase transfer catalysis (PTC) (conc. NaOH/$HCCl_3$/methyltrioctylammonium chloride (Aliquat 336)) to afford (±)-**3a**. In the analogous reaction with $HCBr_3$/EtOH (trace) a mixture of **3b**/**4b** (92 : 8) is formed after 10 min (30–40% conversion); furthermore, a *cis*/*trans*-isomerism of the alkene occurred (**1** : **2** ≈ 8 : 9). After 30 min (80–90% conversion), **3b** and **4b** are present in the ratio 77 : 23, and the unreacted alkene consists to ca. 90% of **2**. Upon being stirred with tetrabutylammonium bromide/NaOH or with Aliquat 336/NaOH in CD_2Cl_2, *trans*-cyclooctene **1** does not rearrange into **2**. Under these reaction conditions, **3b** is also stable, and the course of the reaction is not affected by atmospheric oxygen.



a, X = Cl; **b**, X = Br

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The results found are consistent only with the occurrence of intermediates ($IN_{1,2}$) in the course of the reaction, as sketched in Scheme 1. Upon retro-cleavage, the high-energy IN_1 is converted essentially into the less strained **2**. Moreover, under PTC conditions the reversibility of IN-formation may be particularly propitious since the carbene generation is also a reversible process[13]:

$$\text{Preceding PTC steps} \rightleftharpoons NR_4^{\oplus}CBr_3^{\ominus} \rightleftharpoons NR_4^{\oplus}Br^{\ominus} + CBr_2$$

Apparently the IN_1 formed from **1** and the less reactive CCl_2 is lower in energy and, hence, in this instance, further reaction to **3a** wins out over retro-reaction to give **2**. Presumably IN_1 is not a diradical, since the very sensitive 1,1-dicyclopropylethene does not give rearranged products with CBr_2[14]; in addition, one is certain today that triplet CBr_2[15] does not occur in reactions of this type[16]. IN_1 and IN_2 must be charge-transfer complexes[17]. This would account also for the occasionally observed 1,4-addition of CX_2 to dienes, which according to calculations[18] cannot occur directly.

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[11] **3a**: m.p. = 28 °C (petroleum ether); b.p. = 60 °C/0.1 torr (kugelrohr); ^{1}H-NMR ($CDCl_3$): $\delta = 1.0$–1.25 (m, 6H), 1.45–1.6 (m, 2H), 1.9–2.1 (m, 4H), 2.2–2.3 (m, 2H). **4a**: ^{1}H-NMR: $\delta = 1.1$–1.3 (m, 2H), 1.3–1.7 (m, 10H), 1.95–2.1 (m, 2H).—**3b**: m.p. = 44 °C (petroleum ether, lit. [8]: 43.5–44 °C); ^{1}H-NMR: $\delta = 1.0$–1.15 (m, 4H), 1.15–1.25 (m, 2H), 1.4–1.6 (m, 2H), 1.9–2.1 (m, 4H), 2.25–2.35 (m, 2H).—**4b**: ^{1}H-NMR: $\delta = 1.1$–1.25 (m, 2H), 1.3–1.7 (m, 10H), 2.0–2.1 (m, 2H).
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[17] Unfortunately, no alternative method of generating CBr_2 can be used here (cf. [15, 16]). An experiment in the presence of excess cumene (radical scavenger and competitor for CBr_2) resulted in the following: After 75 min, the product of insertion, 1,1-dibromo-2-methyl-2-phenylpropane, was formed in high yield. **1** and **2** were consumed, and **3b/4b** were present in the ratio 34:66 (!). This result also provides evidence against involvement of a radical process, and the participation of IN_1/IN_2 is further corroborated by the fact that the re-formed CBr_2 is now trapped by both NR_4Br and cumene.
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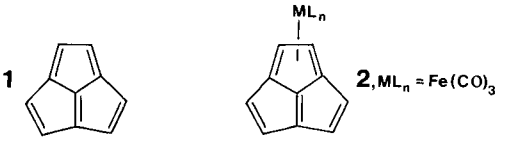
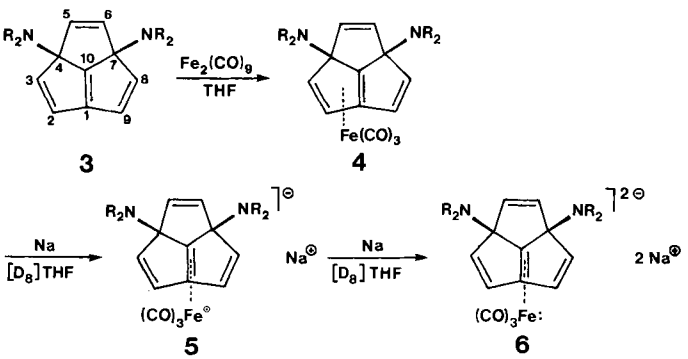
Novel Tricarbonyl(η^4-dihydroacepentalene)iron Complexes and Tricarbonyl(η^2-dihydroacepentalene)ferrates(−2)**

By *Holger Butenschön* and *Armin de Meijere**

Otherwise extremely unstable and/or reactive cyclic polyenes such as unsubstituted cyclobutadiene and pentalene have been isolated as transition-metal complexes[1,2]. No reports have appeared yet on the application of this principle to generate acepentalene **1** (cyclopenta[*cd*]pentalene). Whereas **1** has long been predicted to have a triplet ground state[3], complexes of type **2** should be closed-shell systems[4].



Since the 4,7-bis(dialkylamino)tricyclo[5.2.1.0^{4,10}]deca-1(10),2,5,8-tetraenes (2a,6a-bis(dialkylamino)-2a,6a-dihydroacepentalenes) **3** are readily accessible from 1,4,7-trichloro- and 1,4,7-tribromotriquinacenes and secondary amines[5], we tested whether **3** could be complexed and subsequently defunctionalized. Tricarbonyl(η^4-diene)iron complexes **4** were indeed obtained from **3** and $Fe_2(CO)_9$ in tetrahydrofuran (THF) and were isolated as yellow or orange oils (yields 24–60%) by column chromatography. The compounds were fully characterized by IR, mass, ^{1}H-NMR and ^{13}C-NMR spectroscopy (see Table 1). Although there is no conclusive evidence, the $Fe(CO)_3$ group is most probably oriented *trans* to the two dialkylamino groups. The complexes **4** are new representatives of a class with cross-conjugated triene units and their ^{1}H-NMR data are in accord with those of the few known examples[6]. The conceivable degenerate metallotropic rearrangement[4] of **4** was not observed in **4b** at temperatures up to +150 °C, above which decomposition occurred.



In order to enable the dialkylamino groups to leave, complexes **4a** and **4b** were reduced with sodium and monitored by NMR spectroscopy[7]. In each case, the yellow color changed within 3 h to a deep green, and no NMR signals were detectable at this stage. The apparently para-

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magnetic species thus generated from **4b** did, however, show a broad ESR signal at $g = 2.01598$, which indicates substantial unpaired electron spin density at the iron atom[8]. The green radical is persistent for several weeks if the solution is removed from the sodium. Further contact with the metal causes the solution to become yellow again within 15 h; no further change was observed after 3 d.

Table 1. Dihydroacepentalene complexes: reaction conditions, yields, characteristic data (δ_{TMS}).

4a: **3a** + 7.5 $Fe_2(CO)_9$, THF, 25°C, 3 d, 64%, bright yellow oil.—IR (film): 3050, 2975, 2045 (CO), 1985 (CO), 1955 (CO), 1205, 1070, 760 cm^{-1}.—UV (THF): $\lambda_{max}(\log\varepsilon) = 238$ (sh, 3.982), 313 (4.011), 361 (3.807).—^{1}H-NMR (270 MHz, $CDCl_3$): $\delta = 0.97$ (t, 6H, 2′-H, $^3J_{1',2'} = 6.8$ Hz), 1.05 (t, 6H, 2″-H, $^3J_{1'',2''} = 7.2$ Hz), 2.40—2.75 (m, 8H, 1′-H, 1″-H), 3.70 (d, 1H, 3-H, $^3J_{2,3} = 3.1$ Hz), 5.23 (d, 1H, 2-H), 5.76 (d, 1H, 6-H, $^3J_{5,6} = 6.0$ Hz), 5.93 (d, 1H, 5-H), 6.51 (d, 1H, 8-H, $^3J_{8,9} = 5.5$ Hz, AB system), 6.56 (d, 1H, 9-H).—^{13}C-NMR (100.63 MHz, $CDCl_3$): $\delta = 14.0$ (q, C-2′, $^1J_{C,H} = 125.3$ Hz), 14.8 (q, C-2″, $^1J_{C,H} = 125.3$ Hz), 44.2 (t, C-1′, $^1J_{C,H} = 131.0$ Hz), 45.4 (t, C-1″, $^1J_{C,H} = 131.0$ Hz), 77.0 (dd, C-2, $^1J_{C,H} = 177.7$ Hz, $^2J_{C,H} = 4.1$ Hz), 78.3 (s, C-4), 78.4 (dd, C-3, $^1J_{C,H} = 168.7$ Hz, $^2J_{C,H} = 6.5$ Hz), 83.5 (s, C-7), 88.6 (s, C-10), 116.1 (bs, C-1), 125.5 (dd, C-6, $^1J_{C,H} = 170.9$ Hz, $^2J_{C,H} = 2.8$ Hz), 137.0 (dd, C-5, $^1J_{C,H} = 167.1$ Hz, $^2J_{C,H} = 2.6$ Hz), 141.2 (d, C-8, $^1J_{C,H} = 164.2$ Hz), 147.3 (d, C-9, $^1J_{C,H} = 164.9$ Hz), 212.3 (s, CO).—MS (70 eV): $m/z = 410$ ($M^{\oplus}$, 2%), 255 ($M^{\oplus} - 3\,CO - NEt_2 + H$, 100%).

4b: **3b** + 5 $Fe_2(CO)_9$, THF, 25°C, 1 d; 70%, bright yellow oil.

4c: **3c** + 7.5 $Fe_2(CO)_9$, THF, 25°C, 1 d; 24%, orange oil.

4d: **3d** + 7.5 $Fe_2(CO)_9$, THF, 25°C, 3 d; 26%, yellow oil.

4e: **3e** + 5 $Fe_2(CO)_9$, THF, 25°C, 3 d; 4% (not optimized; losses upon column chromatography), bright yellow oil.

5b: green, persistent.—ESR (9.236 GHz, [D$_8$]THF): $g = 2.01598$ (bs).

6a: yellow.—^{1}H-NMR (270 MHz, [D$_8$]THF): $\delta = 0.99$ (t, 12H, 2′-H, $^3J_{1',2'} = 7.0$ Hz), 2.73 (mc, 4H, 1′-H, $^2J_{1'a,1'b} = -14.2$ Hz), 3.38 (mc, 4H, 1′-H), 4.70 (d, 3(8)-H, $^3J_{3(8),2(9)} = 4.9$ Hz), 5.97 (s, 5(6)-H), 6.11 (d, 2(9)-H).—^{13}C-NMR (67.92 MHz, [D$_8$]THF): $\delta = 14.2$ (q, C-2′, $^1J_{C,H} = 124.1$ Hz), 43.7 (t, C-1′, $^1J_{C,H} = 133.7$ Hz), 68.7 (bs, C-10), 78.7 (bs, C-1), 86.6 (bs, C-4(7)), 122.3 (dd, C-5, $^1J_{C,H} = 158.8$ Hz, $^2J_{C,H} = 4.4$ Hz), 136.8 (d, C-2(9), $^1J_{C,H} = 160.2$ Hz), 142.8 (C-3(8), $^1J_{C,H} = 160.1$ Hz), 237.6 (s, CO).

6b: yellow.—^{1}H-NMR (80 MHz, [D$_8$]THF): $\delta = 1.20-1.60$ (m, 2′-H, 3′-H), 2.10—3.20 (m, 1′-H), 4.72 (d, 3(8)-H, $^3J_{2(9),3(8)} = 4.8$ Hz), 5.90 (s, 5(6)-H), 6.16 (d, 2(9)-H).

The ^{1}H-NMR spectra of the new complexes (see Table 1) are simpler than those of the precursors **4a** and **4b**. Both this and the number of ^{13}C-NMR signals indicate the presence of a plane of symmetry. The number, the chemical shifts, and the multiplicity of the ^{13}C signals are consistent only if the new complexes have structures of the 1,10-η^2-type **6**. In particular, the resonances of the quarternary olefinic carbon atoms C-1/C-10 at 78.7/68.7 and the low-field value of the carbonyl group at $\delta = 237.8$[9] corroborate the structure as tricarbonyl(olefin)ferrate(−2) **6**. All attempts to isolate these ionic complexes, which are extremely oxygen sensitive, have failed so far.

6a and **6b** are the first spectroscopically characterized representatives of this class of compounds. The few reports on the reduction of tricarbonyl(diene)iron complexes only describe indirect evidence for such ferrate complexes from cyclic voltammetry and polarography[10]. The cyclic voltamogram of **4a** shows two irreversible reduction waves at −2.19 and −2.63 V (vs. SCE). This proves the intermediacy of a radical anion as detected in the sodium reductions.

It appears noteworthy that upon reduction of **4** only the 1,10-η^2-complexes **6** are formed and not the less symmetric 2,3-η^2-isomers. This may be due to a favorable stabilization of the symmetric intermediate **5**. The well-known reduction of $Fe(CO)_5$ with sodium to afford disodium tetracarbonylferrate(−2)[11] in the presence of benzophenone as an electron transfer catalyst[12] thus finds its counterpart in the formation of **6** from **4**, where the tetraenic ligand may act as the electron-transfer catalyst.

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Homocyclobutadienes and Cyclopropenes by Reaction of a Stable Cyclobutadiene with Diazo Compounds**

By *Uwe-Josef Vogelbacher, Philipp Eisenbarth*, and *Manfred Regitz**

Bicyclo[2.1.0]pentenes ("homocyclobutadienes") are prepared by irradiation of 1,3-cyclopentadienes; they are thermally unstable and undergo electrocyclic retro-reactions even at room temperature[1]. Herein, we report a novel entry to this class of compounds: Reaction of the cyclobutadiene **1** with diazo compounds leads, inter alia, to formation of the dihydropyrazoles **2**, whose photolysis furnishes thermally stable homocyclobutadienes. The scope of this synthetic strategy depends upon the pattern of substitution in the diazo compounds and is restricted, by an as yet unknown diazoalkane reaction, to cyclopropenylazines.

The reaction of **1**[2] with diazomethane (fourfold excess) is extraordinarily rapid, but in no way specific. [3 + 2]-Cycloaddition at the electron-deficient and sterically best accessible double bond dominates, giving the stable dihydropyrazoles **2** (24%) and **3** (30%); cycloaddition at the di-*tert*-butyl-substituted double bond to give **4** also takes place,

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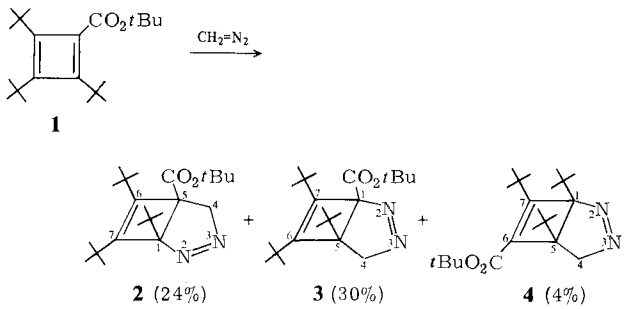
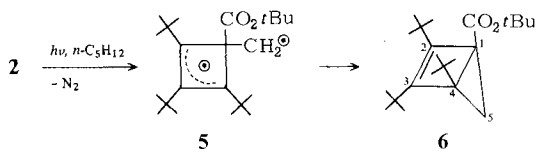
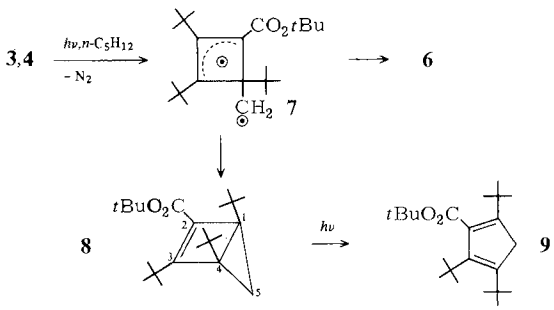
but only to the extent of 4% (separation of products by column chromatography on silica gel with hexane/ether 4:1).



Photolysis of **2** in pentane (Philips HPK 125 W, Pyrex filter) leads quantitatively—presumably via the diradical **5**—to formation of the homocyclobutadiene **6**, which does not isomerize to the corresponding cyclopentadiene, even on distillation (b.p. 110°C/3 × 10^{-6} mbar[3]).



The irradiation of **3** is much more complex, since the diradical **7** cyclizes to the isomeric homocyclobutadienes **6** and **8** (65:35, ^{1}H-NMR). **6** is photostable, whereas the α,β-unsaturated ester **8** slowly rearranges photochemically in an electrocyclic reaction to the cyclopentadiene **9** [^{1}H-NMR, 90 MHz, $CDCl_3$: $\delta = 1.20$, 1.30, 1.36, 1.53 (4 s, each 9 H, *t*Bu, 1,3,4 and ester), 3.05 (s, 2 H, CH_2)]. The same product pattern results on photolysis of **4**, a further proof of its structure and composition.



1 reacts stereospecifically with diazoethane to give exclusively the 4-methyl derivative of **2** (yield 65%, b.p. 125°C/3 × 10^{-6} mbar[3]); the homocyclobutadiene prepared from this compound is also thermally stable (95%, b.p. 125°C/3 × 10^{-6} mbar[3]). Whether the methyl group of the two compounds is *endo*- or *exo*-oriented can not be deduced from the spectroscopic data. The high activation barrier of the homocyclobutadiene/cyclopentadiene isomerization is obviously due to steric reasons.

1 reacts with the doubly acylated or arylated diazomethanes **10** at 20°C in pentane in a novel reaction involving ring contraction[6] to give the yellow (**12a—e, f**) or red cyclopropenylazines (**12d**). We presume that the sterically less favorable cycloaddition is circumvented by attack of

Table 1. Selected physical data of compounds **2**—**4**, **6**, **8**, **12a**, and **12f**.

2: Colorless oil; IR (film): $\nu = 1705$ cm^{-1} (CO); ^{1}H-NMR (90 MHz, $CDCl_3$): $\delta = 1.17$, 1.19, 1.34, 1.48 (4 s, 9 H, *t*Bu-1,6,7, ester), 4.47, 4.98 (2 d, AB system, $J = 18$ Hz, 2 H, 4-H); ^{13}C-NMR (50.28 MHz, $CDCl_3$): $\delta = 27.86$, 28.69, 31.70, 32.50 [$(H_3C)_3C$-1,6,7, ester], 33.88, 34.02, 32.25 [$(H_3C)_3C$-1,6,7], 57.31 (C-5), 77.70 (t, $J = 142.2$ Hz, C-4), 82.04 [$(H_3C)_3C$-ester], 113.36 (C-1), 152.00, 160.54 (C-6/7), 172.49 (CO); MS (18 eV): $m/z = 334$ ($M^{\oplus} - N_2$, 5.9), 222 ($M^{\oplus} - N_2 - 2C_4H_8$, 81%).

3: Colorless crystals, m.p. 85°C; IR (KBr): $\nu = 1705$ cm^{-1} (CO); ^{1}H-NMR ($CDCl_3$): $\delta = 1.03$, 1.21, 1.28, 1.48 (4 s, 9 H, *t*Bu-5,6,7, ester), 4.26, 4.52 (2 d, AB system, $J = 18$ Hz, 2 H, 4-H); ^{13}C-NMR ($CDCl_3$): $\delta = 27.84$, 28.60, 31.60, 32.74 [$(H_3C)_3C$-5,6,7, ester], 33-21, 33.82, 34.27 [$(H_3C)_3C$-5,6,7], 62.61 (C-5), 77.29 (t, $J = 139.0$ Hz, C-4); 82.39 [$(H_3C)_3C$-ester], 102.61 (C-1), 156.99, 157.30 (C-6/7), 170.30 (CO); MS (18 eV): $m/z = 362$ ($M^{\oplus}$, 1), 233 ($M^{\oplus} - N_2 - C_4H_9 - CO_2$, 12), 222 ($M^{\oplus} - N_2 - 2C_4H_8$, 55).

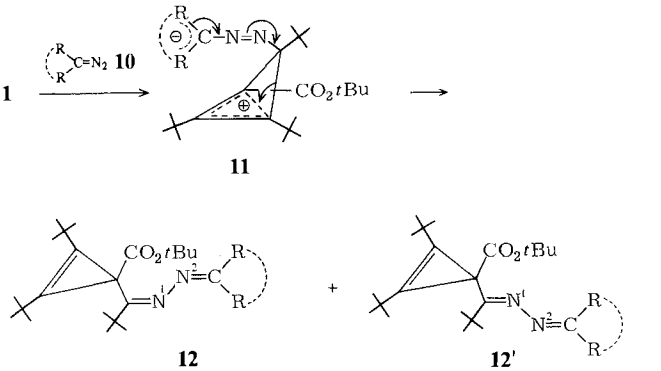
4: Colorless crystals, m.p. 107°C (pentane); IR (film): $\nu = 1700$ (CO), 1635 cm^{-1} (C=C); ^{1}H-NMR ($CDCl_3$): $\delta = 1.11$, 1.27 (each s, 9 bzw. 18 H, *t*Bu-1,5,7), 1.46 (s, 9 H, *t*Bu-ester), 4.07, 4.83 (2 d, AB system, $J_{H,H} = 19.2$ Hz, 2 H, 4-H); ^{13}C-NMR ($CDCl_3$): $\delta = 27.96$, 29.85 [$(H_3C)_3C$-1,5,7, ester], 31-69, 32.48, 35.46 [$(H_3C)_3C$-1,5,7], 82.04 [$(H_3C)_3C$-ester], 115.00 (C-1), 64.75 (C-5), 139.22 (C-6), 160.78 (C-7), 166.72 (CO).

6: Colorless oil; IR (film): $\nu = 1705$ cm^{-1} (CO); ^{1}H-NMR ($CDCl_3$): $\delta = 1.12$, 1.15, 1.17, 1.44 (4 s, 9 H, *t*Bu-2,3,4, ester), 2.00, 2.23 (2 d, AB system, $J = 3.4$ Hz, 2 H, 5-H); ^{13}C-NMR ($CDCl_3$): $\delta = 27.94$, 29.41, 31.54, 31.62 [$(H_3C)_3C$-2,3,4, ester], 31-94 (C-4), 34.24, 34.35, 34.43 [$(H_3C)_3C$-2,3,4], 46.94 (C-1), 52.84 (dd, $J = 148.2$, 166.4 Hz, C-5), 80.00 [$(H_3C)C$-ester], 154.01, 155.90 (C-2/3), 172.78 (CO).—5-Methyl derivative of **6**: colorless oil; IR (film): $\nu = 1700$ cm^{-1} (CO); ^{1}H-NMR ($CDCl_3$): $\delta = 1.12$, 1.15, 1.20, 1.47 (4 s, 9 H, *t*Bu-2,3,4, ester), 1.28 (d, $J = 6.6$ Hz, 3 H, 5-Me), 2.97 (q, $J = 6.6$ Hz, 1 H, 5-H).

8: Colorless oil; ^{1}H-NMR ($CDCl_3$): $\delta = 1.11$, 1.12, 1.17, 1.44 (4 s, 9 H, *t*Bu-1,3,4, ester), 1.78, 2.30 (2 d, AB system, $J = 3.2$ Hz, 2 H, 5-H).

12a: IR (film): $\nu = 1718$, 1672 cm^{-1} (CO); ^{1}H-NMR ($CDCl_3$): $\delta = 1.25$ (s, 9 H, *t*Bu-azomethine), 1.26 (s, 18 H, *t*Bu-2/3), 1.40 (s, 9 H, *t*Bu-ester), 2.35, 2.47 (2 s, 3 H, Me-acetyl); ^{13}C-NMR ($CDCl_3$): $\delta = 25.98$, 30.48 (CO—CH_3), 27.85, 28.53, 30.03 [$(H_3C)_3C$-2/3, azomethine, ester], 32.36, 39.60 [$(H_3C)_3C$-2/3, azomethine], 39.10 (C-1), 80.23 [$(H_3C)_3C$-ester], 119.30 (C-2/3), 157.80 (C=N), 173.36 (CO-ester), 177.10 (C=N), 197.20, 201.42 (CO-acetyl).

12f/12'f (*E*/*Z*-isomers): IR (KBr): $\nu = 1712$ cm^{-1} (CO); ^{1}H-NMR ($CDCl_3$): $\delta = 1.08$, 1.29 (2 s, together 9 H, ratio 50:50, *t*Bu-azomethine), 1.29 (2, 18 H, *t*Bu-2/3), 1.40, 1.51 (2 s, together 9 H), ratio 50:50, *t*Bu-ester), 7.1—8.6 (m, 8 H, aromat. H); ^{13}C-NMR ($CDCl_3$): $\delta = 27.05$, 27.76, 28.20, 29.60, 30.11, 30.43 [$(H_3C)_3C$-2/3, azomethine, ester], 31.90, 32.80, 38.53, 39.60 [$(H_3C)_3C$-2/3, azomethine], 37.64, 42.60 (C-1), 79.32, 80.34 [$(H_3C)_3C$-ester], 118.18 (C-2/3), 120—142 (aromat. C), 147.78, 157.60, 165.03, 173.88 (C=N), 175.08, 175.31 (CO); MS (70 eV): $m/z = 512$ ($M^{\oplus} \leq 1$), 455 ($M^{\oplus} - C_4H_9$, 3).



10, 11, 12	a	b	c	d	e	f
	COMe	CO_2Me	COPh		Ph	
	COMe	CO_2Me	COPh		Ph	
	65	61	45	56	51	52
Yield [%]	–	–	106	142	129	60
M.p. [°C]	145/3×10^{-6}	160/10^{-5}	–	–	–	–
B.p. [°C/mbar]	[3]	[3]				

the terminal, electrophilic nitrogen atom of **10** at C-2 of the cyclobutadiene[4]; initially the homocyclopropenylium betaines **11**[5] are formed in which the charge is optimally stabilized.

The constitution of the azines is supported not only by their colors and analytical data but, in particular, by the ^{13}C-NMR spectra (50.28 MHz, $CDCl_3$); the spectra show, inter alia, separated signals for two azomethine C atoms ($\delta = 141.10-177.04$); the olefinic three-membered ring atoms ($\delta = 117.89-119.30$) as well as the two C-type atoms of the *tert*-butyl groups attached to this ring, and the sp^3 cyclopropene C-atom ($\delta = 37.64-42.60$) each give only one signal. The signals of the cyclopropene C atoms are virtually identical with those observed for *tert*-butyl(1,2,3-tri-*tert*-butyl-2-cyclopropenyl)diazoacetate[2].

Since the diazomethane substituents are identical, the azines occur only as *E*/*Z* isomers **12** and **12'**, as also follows from the NMR spectra in the case of **12e** and **12f** (see Table 1; the isomeric ratios are 60:40 and 50:50, respectively). That the same phenomenon is not observed in the case of **12a**—**12d** can only be ascribed to a rapid inversion at N-1, enforced by the other half of the azomethine moiety, which is a stronger electron-acceptor[7].

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1 83747-03-9; **2** 91181-02-1; **3** 91181-03-2; **4** 91181-04-3; **6** 91181-05-4; **8** 91181-06-5; **9** 91181-01-6; **10a** 29397-21-5; **10b** 6773-29-1; **10c** 2085-31-6; **10d** 85-41-6; **10e** 883-40-9; **10f** 832-80-4; **12a** 91181-08-7; **12b** 91181-09-8; **12c** 91181-10-1; **12d** 91181-11-2; **12e** 91181-12-3; **12e'** 91181-14-5; **12f** 91181-13-4; **12f'** 91181-15-6

[1] The half-life of unsubstituted bicyclo[2.1.0]pentane (CCl_4, 20°C) is ca. 2 h: J. I. Brauman, L. E. Ellis, E. E. van Tamelen, *J. Am. Chem. Soc. 88* (1966) 846; methyl-substituted bicyclo[2.1.0]pentenes behave analogously: W. R. Roth, F.-G. Klärner, H.-W. Lennartz, *Chem. Ber. 113* (1980) 1818; F.-G. Klärner, F. Adamsky, *ibid. 116* (1983) 299.

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[3] Kugelrohr distillation.

[4] The mass spectra of **12c—f** support this by the fragments *m/z* = 251 (7—13%) and 194 (19—100%), that is the *tert*-butoxycarbonyl-di-*tert*-butylcyclopropenylium ion and that of the same fragment minus an isobutene moiety.

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Facile Synthesis of Heteroalkenes $CF_3E{=}CF_2$ (E = P, As)**

By *Joseph Grobe** and *Duc Le Van*

The phosphaalkene $CF_3P{=}CF_2$ **2a** was previously prepared by base-induced cleavage of HF from $(CF_3)_2PH$[1] or by base-catalyzed reaction of dimethylzinc with $(CF_3)_2PH$[2], i.e. by methods which afford **2a** in impure form or in low yield. On re-investigating the decomposition reaction of the stannanes **1**[3], we have now discovered a simple method for the quantitative synthesis of **2**.

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[**] Reactive E=C–(p-p)π Systems, Part 1. This work was supported by the Landesamt für Forschung des Landes Nordrhein-Westfalen.

$$Me_3SnE(CF_3)_2 \xrightarrow[-Me_3SnF]{300-340\,^\circ C} CR_3E{=}CF_2$$
1 **2**

a, E = P; **b**, E = As

The heteroalkenes **2** are formed on thermolysis of **1** at 10^{-3} torr in a pyrolysis tube and are quenched from the gas phase at −196°C. Pyrolysis experiments at the inlet of a mass spectrometer showed that an optimal temperature range for this process is 300—340°C. Unreacted **1** is repeatedly fed through the hot zone until the conversion into **2** is complete[4]. The phosphaalkene **2a** can be recondensed in a high vacuum at 10^{-3} torr without any detectable loss, whereas the new arsaalkene **2b** rapidly dimerizes or polymerizes. Despite its high reactivity, **2b** could be unequivocally characterized by its ^{19}F-NMR spectrum at −110°C (Fig. 1) and finally identified by its dimerization products.

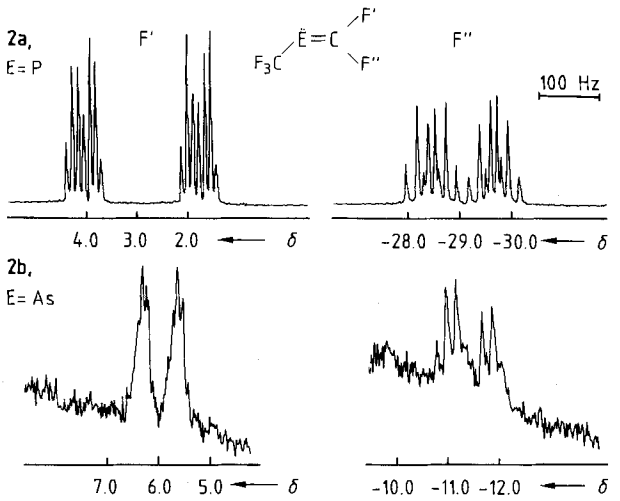
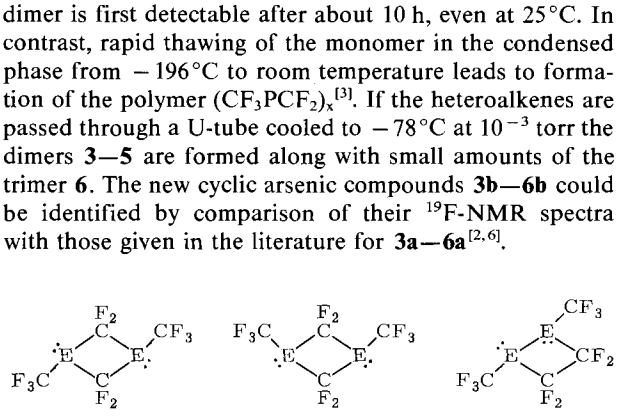


Fig. 1. Sections from the ^{19}F-NMR spectra of **2a** (top) and **2b** (bottom); in each case the region for the CF_2-group is shown.

Apart from the molecular peaks [**2a**: *m/z* 150 ($M^\oplus$); **2b**: *m/z* 194 ($M^\oplus$)] the mass spectra of the two compounds show similar degradation patterns. $CF_3As{=}CF_2$ is the smallest As=C–(p-p)π-system so far isolated[5].

The kinetic stability observed for **2a** in ca. 10% organic solutions (e.g. toluene, pentane) is surprising: thus, the dimer is first detectable after about 10 h, even at 25°C. In contrast, rapid thawing of the monomer in the condensed phase from −196°C to room temperature leads to formation of the polymer $(CF_3PCF_2)_x$[3]. If the heteroalkenes are passed through a U-tube cooled to −78°C at 10^{-3} torr the dimers **3**—**5** are formed along with small amounts of the trimer **6**. The new cyclic arsenic compounds **3b**—**6b** could be identified by comparison of their ^{19}F-NMR spectra with those given in the literature for **3a**—**6a**[2,6].



3 **4** **5**

a, E = P; **b**, E = As

The four-membered heterocycles **3** with *trans*-oriented CF_3 groups are the major products of the [2+2]-cycloaddition, whereas only small amounts of the *cis*-compounds **4** and head-to-head isomers **5** are formed; the product patterns for phosphorus and arsenic compounds under the same reaction conditions are different.

3a : **4a** : **5a** : **6a** = 85 : 9 : 2 : 4
3b : **4b** : **5b** : **6b** = 64 : 21 : 3 : 12

This could be due to the greater activity of **2b**, which also facilitates reactions between monomers less favorably oriented with respect to each other. In solution, the *cis*-isomers **4a** and **4b** are transformed only very slowly into the more stable *trans*-isomers **3a** and **3b**, respectively.

The ^{19}F-NMR spectrum of **3b** is especially simple; it shows two signal groups in the intensity ratio 3 : 2 for the two CF_3 moieties (quintet) and the CF_2 ring members (septet), thus indicating a planar ring structure (see Table 1).

Table 1. ^{19}F-NMR data of **2a** and **2b**—**6b** [a]. For F′ and F″, see Figure 1.

2a: $\delta = -44.4$ (ddd) CF_3, 2.9 (ddq) F′, −29.1 (ddq) F; $^2J(PF) = 57.4$, $^2J(PF') = 192.0$, $^2J(PF'') = 103.0$, $^2J(F'F'') = 29.2$, $^4J(FF') = 10.0$, $^4J(FF'') = 18.0$

2b: $\delta = -41.2$ (dd) CF_3, 6.0 (dq) F′, −11.4 (dq) F″; $^2J(F'F'') = 60.0$, $^4J(FF') = 8.5$, $^4J(FF'') = 17.0$

3b: $\delta = -44.3$ (quint) CF_3, −90.4 (sept) CF_2; $^4J(FF) = 7.5$

4b: $\delta = -43.3$ (tt) CF_3, CF_2: AB system, $\delta_A = -77.8$, $\delta_B = -96.2$; $^2J(F(AB)) = 260$, $^4J(FF) = 10.5$, 4.5

5b: $\delta = -39.6$ (quint, br.) CF_3, −92.9 (br.) CF_2; $^4J(FF) = 7.0$

6b: $\delta = -42.1$ (quint), −41.1 (m, br.) CF_3; −72.4 (m, br.), −74.1 (m, br.), −80.7 (m, br.) CF_2; $^4J(FF) = 7.0$

[a] The data for **3a**—**6a** agree with those quoted in the literature [2, 6]. ^{19}F-NMR data (84.66 MHz) **2a**: [D_8]toluene, −60°C; **2b**: [D_6]dimethyl ether, −110°C; **3b**—**6b**: [D_8]toluene, 28°C; external standard: CCl_3F: *J* [Hz]. Data for **2a** in [1] not complete.

The elimination of Me_3SnF could also be exploited for the preparation of other heteroalkenes. Thus, the novel compound $Me_3SnP{=}CF_2$ is formed on thermolysis of $(Me_3Sn)_2PCF_3$, and the known, unstable thia- and selenaalkenes $E'{=}CF_2$ (E′ = S, Se)[7] can be obtained quantitatively from $Me_3SnE'CF_3$.

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[4] Procedure: **1a** (3.33 g, 10 mmol) or **1b** (1.9 g, 5 mmol) is passed by suction (0.001 torr) through a pyrolysis tube 250 mm in length and 18 mm diameter (**1a** at 300°C, **1b** at 340°C). **1a** or **1b** are condensed in a cold trap at −78°C, **2a** or **2b** at −196°C. The less volatile $(Me_3SnF)_n$ separates out immediately after the hot zone. Unreacted **1a** or **1b** is re-pyrolyzed (complete reaction after ca. five cycles). **2a** and **2b** are each formed quantitatively; the isolable yields are 1.38 g (92%) **2a** and (in [D_6]dimethyl ether at −110°C) ca. 10% **2b** together with ca. 90% **3b**—**6b**.
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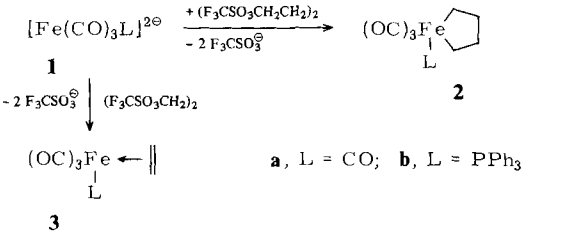
Facile Synthesis of Highly Reactive Ferracycloalkanes**

By *Ekkehard Lindner**, *Eckard Schauss*, *Wolfgang Hiller*, and *Riad Fawzi*

Dedicated to Professor Walter Rüdorff on the occasion of his 75th birthday

Metallacyclopentanes occur as reactive intermediates in numerous metal-catalyzed cycloadditions and cycloreversions of alkenes. For model studies of such systems, several five-membered metallacycles of some transition metals have been prepared or implicated as intermediates[1]. Although *Stone* et al.[2] and *Wilkinson* et al.[3] described perfluorinated ferracyclopentane, $(OC)_4FeC_4F_8$, as early as 1961, only now have we succeeded, for the first time, in synthesizing the parent compound, tetracarbonylferracyclopentane **2a**. The stereochemistry of the ring closure reaction of $(\eta^2\text{-}C_2H_4)_2Fe(CO)_3$[4] to **2a** has been analyzed



theoretically by *Hoffmann* et al[5]. The nucleophilic elimination-cycloaddition of tetramethylenebis(trifluoromethanesulfonate)[6] with $[Fe(CO)_4]^{2\ominus}$ now facilitates a straightforward route to the extremely volatile ferracyclopentane **2a**, which precipitates at −78°C from *n*-butane as colorless crystals that are heat- and air-sensitive and readily soluble in all organic solvents.

X-ray structure analysis[7] indicates that the more stable **2b**[8], which is obtained analogously, has a twist conformation (Fig. 1). Because of conformational chirality, C6 and C7 are disordered[9]. This was taken into consideration in calculating the structure by introducing split positions ob-

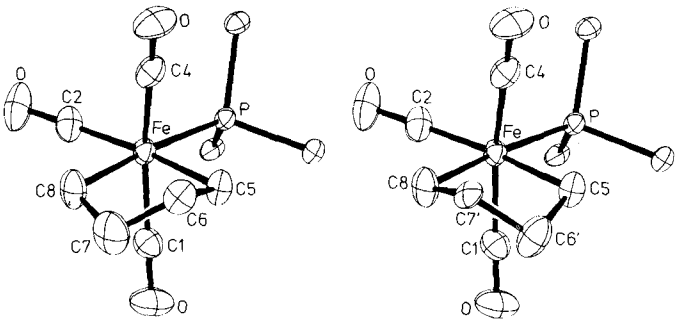


Fig. 1. Molecular structure of the enantiomers in the crystal of **2b** in their statistical distribution. Selected distances [pm] and angles [°]: Fe-C5 214.1(4), Fe-C8 210.7(4), C5-C6 153.9(11), C5-C6′ 154(2), C6-C7 151(2), C6′-C7′ 153(3), C7-C8 149.5(10), C7′-C8 157(2), C1-Fe-C4 162.0(2), C5-Fe-C8 82.5(2), C5-C6-C7 108(1), C5-C6′-C7′ 105(2), C6-C7-C8 109(1), C6′-C7′-C8 105(2).

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tained by a difference Fourier synthesis. The C6C7 and C6′C7′ distances correspond to the length of a single bond. **2a**, **b** were further characterized by elemental analysis as well as by mass, IR, and $^{13}C\{^1H\}$-NMR spectra (Table 1). In **2a**, the C atoms in the α- and β-positions, respectively, are magnetically equivalent. In contrast, because of the PPh_3 ligand, in **2b** four signals occur which are split into doublets for C5, C7, and C8. The larger coupling constant is ascribed to the *trans*-C8-Fe-P group. The assignment of the signals is corroborated by studies of **2a**, **b** in which the β-positions of the ferracyclopentanes were labeled by deuterium (Table 1).

Table 1. Spectroscopic data and melting points for **2a**, **2b**, and **3b**.

	2a	**2b**	**3b**
IR [cm^{-1}]	2096 m-s		
ν(CO) [a]	2032 s	2042 w	2024 vs
	2021 vs	1977 vs	1965 s
	2010 s-vs	1972 sh	1935 s-vs
$^{13}C\{^1H\}$-NMR δ	22.1 (s, C5,8)	21.0 (d, C8) [c]	37.4(s,C5,6)
[b]	36.6 (s, C6,7)	26.8 (d, C5) [d]	
		35.0 (d, C7) [e]	
		37.3 (s, C6)	
	205.1 (s, C2,3)	212.1 (d, C2) [f]	216.3(s,C2,3)
	212.2 (s, C1,4)	218.0 (d, C1,4) [g]	216.6(s,C1)
MS (m/z)	224 ($M^{\oplus}$)	458 ($M^{\oplus}$) [h]	430 ($M^{\oplus}$)
M.p. [°C]	−35 (decomp.)	79	120 (decomp.)

[a] In *n*-hexane. [b] In $CDCl_3$, 20.115 MHz, δ-value rel. TMS. [c] $^2J(CP)=10.2$ Hz. [d] $^2J(CP)=5.1$ Hz. [e] $^3J(CP)=8.9$ Hz. [f] $^2J(CP)=10.0$ Hz. [g] $^2J(CP)=14.0$ Hz. [h] FD-MS (8 kV).

In the presence of CO, **2a** is remarkably stable, and the expected formation of cyclopentanone is observed only at 20°C[10]. In the absence of CO, **2a** decomposes already at −35°C to afford $Fe_3(CO)_{12}$ as well as *cis*- and *trans*-butene in the molar ratio 1:2.

The ethene complexes **3a**[11] and **3b**[5] can be obtained analogously and have been characterized by mass, IR, and $^{13}C\{^1H\}$-NMR spectroscopy (Table 1). **3a**[11] has previously been prepared from $Fe_2(CO)_9$ and C_2H_4, a method associated with tedious, laborious separation from $Fe(CO)_5$. X-ray structure analysis of **3b**[7] confirms the predicted equatorial arrangement[12] of ethene (Fig. 2).

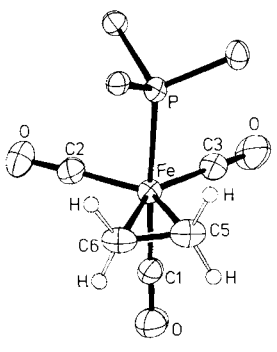

Fig. 2. Molecular structure of **3b** in the crystal. Selected distances [pm] and angles [°]: Fe-C5 209.5(7), Fe-C6 210.2(7), C5-C6 139.8(8); Fe-C5-C6 70.8(4), Fe-C6-C5 70.3(4), C5-Fe-C6 38.9(2), C2-Fe-C3 112.2(3).

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[7] Triclinic crystals of **2b** (space group $P\bar{1}$) from *n*-butane. Refinement in the non-centrosymmetric space group P1 did not lead to an improvement of the structure model and confirmed the assumption of a disorder of atoms C(6) and C(7). Lattice constants at 183 K ($Mo_{K\alpha}$ radiation): $a=969.4(4)$, $b=976.4(6)$, $c=1348.9(5)$ pm, $\alpha=103.75(5)$, $\beta=108.77(3)$, $\gamma=70.16(3)°$, $Z=2$, $\rho_{calc.}=1.352$ g/cm³. Structure solved with MULTAN, $R=0.039$, 3833 reflections with $I\geq 3\sigma(I)$. Monoclinic crystals of **3b** (C2/c) from *n*-pentane. Lattice constants at 193 K ($Mo_{K\alpha}$ radiation): $a=2350.4(3)$, $b=1425.4(3)$, $c=1917.1(5)$ pm, $\beta=140.99(4)°$, $Z=8$, $\rho_{calc.}=1.414$ g/cm³. Structure solved with MULTAN, $R=0.039$, 1639 reflections with $I\geq 3\sigma(I)$. Further details on the crystal structure investigations can be obtained from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, by quoting the depository number CSD 50942, the names of the authors, and the journal citation.
[8] Procedure: A solution of 10 mmol $(F_3CSO_3CH_2CH_2)_2$ or $(F_3CSO_3CH_2)_2$ in 150 mL dimethyl ether is added dropwise at −50°C to a suspension of **1a**, **b** (10 mmol) in 100 mL dimethyl ether. After 12 h, the dark red solution is concentrated to a third at −80°C in vacuo and diluted with *n*-butane to the original volume. After the residue is decanted off, the solution is concentrated in vacuo until the colorless (**2a**, **3a**) or yellow (**2b**, **3b**) compounds precipitate; purification follows by recrystallization from *n*-butane (**2a**, **3a**: −78°C) and *n*-pentane (**2b**, **3b**: −25°C), respectively. Yields 60–90%.
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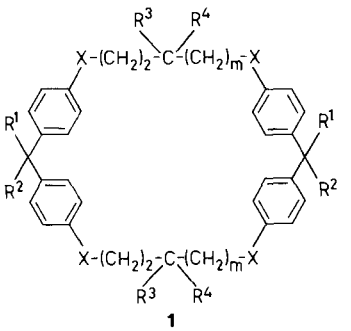
[10] F.-W. Grevels, D. Schulz, E. Koerner von Gustorf, *Angew. Chem. 86* (1974) 558; *Angew. Chem. Int. Ed. Engl. 13* (1974) 534.
[11] a) H. D. Murdoch, E. Weiss, *Helv. Chim. Acta 46* (1963) 1588; b) D. D. Beach, W. L. Jolly, *Inorg. Chem. 22* (1983) 2137.
[12] a) M. I. Davis, C. S. Speed, *J. Organomet. Chem. 21* (1970) 401; b) T. A. Albright, R. Hoffmann, J. C. Thibeault, D. L. Thorn, *J. Am. Chem. Soc. 101* (1979) 3801; c) T. A. Albright, *Tetrahedron 38* (1982) 1339.

Novel Host Structures for the Selective Inclusion of Aromatic and Aliphatic Guests in Aqueous Solution**

By *Fritz Vögtle** and *Walter M. Müller*

Tetraammonium salts of the [n.1.n.1]cyclophane type **1** (m = 1–3, X or R^1–R^4 may contain an $N^{\oplus}$) with units derived from diphenylmethane form an elongated cavity and are suitable, water-soluble host structures for neutral aromatic guest molecules[1].



1

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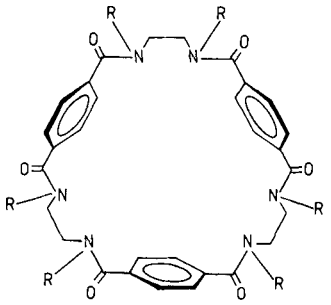
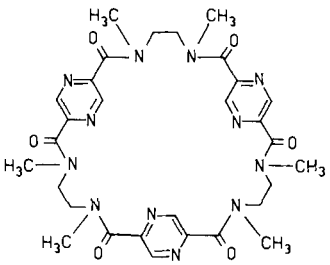
[**] Frau *U. Werner* is thanked for her assistance.

We now report the host structures **2a-c**, which differ principally from **1**, and which are just as effective as hosts. They are marked by their propitious and variable syntheses—starting from standard reagents such as terephthaloyl dichloride, ethylenediamine, and pyridinecarbaldehyde.



2a-d



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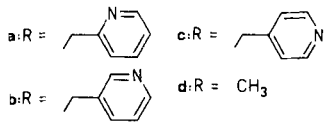


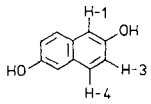
a: R = c: R =

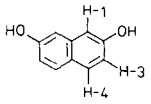
b: R = d: R = CH_3

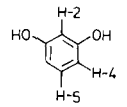
The 30-membered sixfold acid amides **2a-c** of the [6.6.6]paracyclophane type, which are relevant for receptor- and enzyme-model studies, and which have, respectively, six α-, β-, and γ-pyridylmethyl side arms[2], exhibit in aqueous acidic solution (e.g. $pD = 1.2$) similar guest-binding properties as hosts of the type **1**, but have different substrate selectivity (vide infra). The large high-yield shifts of the ^{1}H-NMR signals of the aromatic *guest* molecules (resorcinol, 2,6- and 2,7-naphthalenediol) and of the *host* protons differ little from those caused by the host **1**[3]. In addition, Table 1 contains data on the new macrocycles **2d** and **3**—the latter with pyrazine structural elements—which also function as host compounds.

Under analogous conditions, **2b** induces the largest high-field shifts. A 1:1-mixture of hosts **2b** and **2c** with the guest 2,6-naphthalenediol exhibits predominantly the characteristic high-field shift pattern of the **2b** complex. These differences in the host/guest binding are possibly attributable, inter alia, to the different spatial separation of the six pyridine nitrogen atoms from the formally similar cavity in **2a-c** and to the presence of H bonds between the OH groups of the naphthalenediols and the nitrogen atoms of the pyridine rings, as indicated by inspection of molecular models.

Table 1. ^{1}H-NMR high-field shifts $\Delta\delta$ [ppm] of guest protons by the host compounds **2a—d** and **3** (400 MHz, in D_2O/DCl at $pD = 1.2$ and 21°C. Standard defined as HDO at $\delta = 4.8$. Concentrations: host 2.5×10^{-2} M, guest: 1.25×10^{-2} M). The chemical shifts for the guests are 2,6-naphthalenediol: $\delta = 7.13$ (H-1), 7.06 (H-3), 7.61 (H-4); 2,7-naphthalenediol: $\delta = 7.03$ (H-1), 6.93 (H-3), 7.69 (H-4); resorcinol: $\delta = 6.35$ (H-2), 6.42 (H-4), 7.11 (H-5).



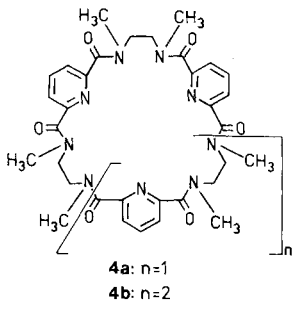




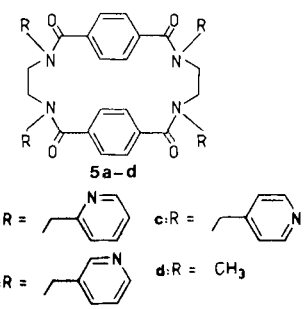
	Guests								
Host	H-1	H-3	H-4	H-1	H-3	H-4	H-2	H-4	H-5
2a	0.61	0.44	0.58	0.52	0.20	0.41	0.27	0.23	0.25
2b	0.76	0.54	0.78	0.64	0.35	0.53	0.42	0.36	0.38
2c	0.61	0.32	0.60	0.63	0.21	0.42	0.26	0.19	0.20
2d	0.34	0.23	0.23	0.26	0.24	0.25	0.21	0.19	0.20
3	0.26	0.26	0.24	0.31	0.30	0.31	0.32	0.32	0.32

Studies of comparable substances corroborate the conclusion that the high-field shifts in the system **2** indicate molecular guest-inclusion in aqueous solution. The methyl-substituted 27- and 36-membered pyridinophanes **4a**, **b**, which are also water-soluble when protonated[4], do not—as pyridine and 2- and 3-methylpyridine—exhibit analogous high-field shifts, although the H/D exchange rate of added phenols is also—if only slightly—accelerated (vide infra): the guest molecules described apparently require an approximately 30-membered macrocycle, such as in ring **2**, but not in **4** or **5**.

Of especial note for the novel host structures **2a-c** is that in addition to aromatic also *aliphatic* guests such as *trans*-1,4-cyclohexanediol, *trans*-1,4-cyclohexanedicarboxylic acid, adamantanecarboxylic acid, and adamantanethiol are dissolved by complexation in aqueous acidic solution. Accordingly, the high-field shifts of the cyclohexane- and adamantane-CH protons can be taken as also indicating the inclusion of those aliphatic guests into the cavity. Inspection of molecular models suggests that the cavity in **2a-c** is more "circular" than in **1**.



4a: n=1
4b: n=2



5a-d

a: R = c: R =

b: R = d: R = CH_3

In contrast to the host system **1**[5], *rapid* H/D-exchange of the 1,5-(1,8)protons of 2,6-(2,7-)naphthalenediol and of the 2-proton of resorcinol occur in the presence of the hosts **2a-c**. We ascribe this to a catalysis effected by the pyridine nitrogen atoms of the side arms[6].

The hosts **2** and the analogously synthesized new ligand **3** are concipated to complex not only neutral guests but also cations, just as in the cocomplexation in enzymes. An illustration of their capacity to bind cations is the ability of the hosts **2** to solvate sodium permanganate into lipophilic phases (CH_2Cl_2), a phenomenon previously known only for efficient crown ethers, cryptands, and podands. Host ligands of the type **2** should also function as catalysts for proton transfers, nucleophilic substitution[7], and as models for NADH[8].

General procedure for the macrocycles using the example of 2a-c

A solution of 40.0 mmol of the corresponding *N,N'*-substituted ethylenediamine (prepared from ethylenediamine and the corresponding pyridine carbaldehyde and subsequent hydrogenation with 5% Pd/$CaCO_3$) in 250 mL benzene is allowed to react at room temperature with a solution of 20.0 mmol terephthaloyl dichloride in 250 mL benzene under high dilution conditions (7 h simultaneous dropwise addition into 1 L benzene). The oligomers, which were extracted with dichloromethane, are separated by chromatography, column chromatography (Al_2O_3, CH_2Cl_2/EtOH as eluent), dry column chromatography (Al_2O_3), or preparative thin-layer chromatography (Al_2O_3, CH_2Cl_2/EtOH as eluent). **2a**: Yield (in each case relative to the dicarboxylic acid dichloride): 1.9%, m.p. = 149—155°C; **2b**: 3.6%, 143—149°C, phase transition 205°C, 271—273°C; **2c**: 1.0%, 163—170°C, phase transition 235°C, 263—266°C; **2d**: 8.2%, 114—123°C; **3**: 7.8%, 115—126°C; **4a**: 16.6%, 123—129°C; **4b**: 7.9%, 132—136°C.

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[1] a) K. Odashima, A. Itai, Y. Iitaka, Y. Arata, K. Koga, *Tetrahedron Lett. 21* (1980) 4347; K. Odashima, K. Koga: *Cyclophanes, Vol. 2*, Academic Press, New York 1983, S. 629; b) F. Diederich, K. Dick, *Angew. Chem. 95* (1983) 730; *Angew. Chem. Int. Ed. Engl. 22* (1983) 715; *Angew. Chem. Suppl. 1983*, 957; c) H. J. Schneider, personal communication; d) J. Winkler, E. Coutouli-Argyropoulou, R. Leppkes, R. Breslow, *J. Am. Chem. Soc. 105* (1983) 7198; e) Y. Murakami, *Top. Curr. Chem. 115* (1983) 107; f) cf. I. Tabushi, K. Yamamura, *ibid. 113* (1983) 145; g) cf. also C. J. Suckling, *J. Chem. Soc. Chem. Commun. 1982*, 661.

[2] Correct elemental analyses, ^{1}H-NMR, and mass spectra were obtained for all the new compounds.

[3] The shifts arise from anisotropic effects between host and guest as well as from the influences of the positive charges on the pyridinium groups; cf. [1b, c].

[4] Since **2** (R = benzyl), in contrast to **2a—c**, is not soluble in acids, analogous inclusions in water are ruled out; cf. F. Vögtle, H. Puff, E. Friedrichs, W. M. Müller, *J. Chem. Soc. Chem. Commun. 1982*, 1398.

[5] Prof. *K. Koga*, Kyoto, is thanked for this personal communication.

[6] Cf. G. W. Kirby, L. Ogunkoya, *J. Chem. Soc. 1965*, 6914, and references cited therein.

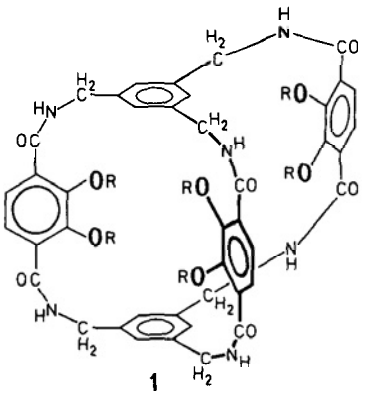
[7] Attempts to hydrolyze lipophilic *p*-nitrophenyl esters in the presence of **2a**, **b** as catalyst in aqueous acidic solution indicate an inhibition attributable either to a strong host/guest binding or to an unfavorable position of the nucleophilic centers of the host.

[8] Cf. R. M. Kellogg, *Top. Curr. Chem. 101* (1982) 111.

Functionalized, Oligocyclic Large Cavities—A Novel Siderophore**

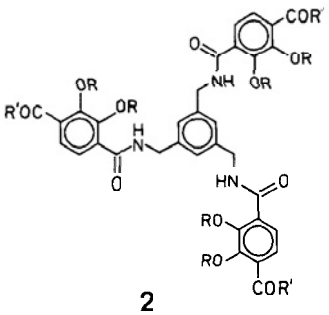
By *Wolfgang Kiggen* and *Fritz Vögtle**

We have succeeded in synthesizing a novel complex ligand-type **1**, which cannot be described as a crown ether, cryptand, or spherand. Moreover, the new ligand is a cage-like macrooligocycle which exhibits a cavity bounded on three sides and has functional groups suitable for complex formation[1].



1

a: R = CH_3 b: R = H



2

a: R = CH_3, R' = CH_3O b: R = CH_3, R' = NaO
c: R = CH_3, R' = Cl d: R = H, R' = HO

The colorless hexalactam **1a** can be synthesized by two routes using high dilution conditions[2] via Stetter cyclization[3]: a) from 2,3-dimethoxyterephthaloyl dichloride[4] and 1,3,5-benzenetriyltris(methaneamine) in 1.5% yield; and b) from the new tris(acid chloride) **2c** and 1,3,5-benzenetriyltris(methaneamine) in 13% yield (790 mg per charge!). The hexamethoxy compound **1a** (decomp. 290°C) dissolves remarkably readily in chloroform, but less well in dichloromethane.

The ^{1}H-NMR spectrum reflects the symmetry of the molecule[5]. The singlet of the methoxy protons is shifted characteristically to high field. On the NMR time scale, the OCH_3 groups apparently rotate relatively unhindered about the *p*-phenylene axis and thus gain access to the anisotropic region of the two 1,3,5-substituted benzene rings. At −109°C the high-field shift is still marked; all signals are broadened. Inspection of space-filling models indicates that not all of the six methyl groups of **1a** can be accommodated *simultaneously* in the interior of the molecule. Accordingly, this provides an explanation why **1a**, unlike other neutral ligands, is not able to solvate inorganic salts into lipophilic phases.

Cleavage of the methoxy groups in **1a** by BBr_3 in dichloromethane liberates the hexahydroxy compound **1b** (decomp. 285°C). **1b** fluoresces intensely bright blue in light of wavelength 366 nm, both in the solid state and in solution in dimethyl sulfoxide. Alkaline solutions are scarcely air sensitive. The FAB mass spectrum of **1b** in a glycerine matrix exhibits a significant $[M+H]^{\oplus}$ peak[6].

Examination of molecular models suggests that in the hexaanion of **1b** an octahedral donor geometry for metal cations is formed; upon complexation, a helical-chiral configuration results (Fig. 1).

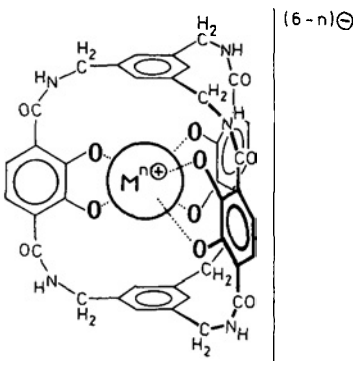


Fig. 1. Octahedral metal complex of **1b**.

"Siderophores" (iron carriers) which contain catechol moieties form octahedral complexes with $Fe^{3\oplus}$[7]. That **1b** is a remarkably stronger complexing ligand emerges from the observation that moist **1b** attacks 18/8 stainless steel, producing a blue-black coloration. Iron and nickel powder are dissolved in minutes, and chromium powder is dissolved within a few hours to form blue-green, green-grey, and pink solutions, respectively, on exposure to air.

Addition of $Fe^{3\oplus}$ salts to a solution of the novel ligand **1b** in water at pH 11 leads to the characteristic red-violet tint ($\lambda_{max} = 544$ nm, $\varepsilon \approx 4680$). For comparison, we prepared from **2a** the colorless, open-chained, hexadentate ligand **2d**, whose solution in water at pH 11—in contrast to **1b**—becomes red-brown ($\lambda_{max} = 508$ nm, $\varepsilon \approx 5120$) upon addition of $Fe^{3\oplus}$ salts. Titrations of the two ligands against $Fe^{3\oplus}$, with UV/VIS monitoring, indicate a 1:1 stoichiometry. Upon acidification of the $Fe^{3\oplus}$-complex solutions of **1b** and **2d**, blue-black compounds precipitate out. The occurrence of a $[(lig)H_3Fe+H]^{\oplus}$ peak in the FAB mass spectrum of the $Fe^{3\oplus}$ complex of **1b** in a diethanolamine matrix[6] corroborates the 1:1 stoichiometry, which suggests the presence of one cation in the cavity, as shown in Figure 1[8]

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[**] This work was supported by the Minister für Wissenschaft und Forschung des Landes Nordrhein-Westfalen.

Extinction measurements indicate that EDTA, even when present in 1000 fold excess (pH 11), cannot compete with the Fe^{III}-complexes of **1b** and **2d**, although the formation constant K_f for the Fe^{III}-EDTA complex is 10^{25}[9]. Finally, the superiority of the ligand **1b** becomes clear from competition experiments with **2d**, in which ca. 70% of the iron(III) ions are complexed by **1b**; however, in order to establish equilibria, the solutions require to be heated for several hours at 100°C.

Our synthetic methodology allows construction of even roomier cavities by using spacers larger than the two 1,3,5-substituted benzene nuclei, e.g. 1,3,5-triphenylbenzene building blocks, as we have previously employed in another connection (cyclophanes)[10]. In this respect, these macrooligocycles are also of interest for chemical reactions in cavity interiors as well as for model studies of receptors with larger guests[1].

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[1] Cf. F. Vögtle, W. M. Müller, *Naturwissenschaften 71* (1984) 148, and literature cited therein.
[2] Cf. L. Rossa, F. Vögtle, *Top. Curr. Chem. 113* (1983) 1.
[3] H. Stetter, E.-E. Roos, *Chem. Ber. 88* (1955) 1390.
[4] F. Dallacker, W. Korb, *Justus Liebigs Ann. Chem. 694* (1966) 98.
[5] **1a**, ^{1}H-NMR (CD_2Cl_2) at 27°C: $\delta = 2.90$ (s, OCH_3), 4.43 (d, $J = 6$ Hz, Aryl-CH_2), 7.41 (s, Aryl-H, 2,4,6), 7.83 (s, Aryl-H, 5,6), 7.88 (t, NH, $J = 6$ Hz); at −109°C: 3.37, 4.58, 7.44, 7.79, 8.17.
[6] Prof. Dr. *F. Röllgen* and Dipl.-Chem. *S. S. Wong*, Bonn, are gratefully thanked for recording the mass spectra and for discussions.
[7] K. N. Raymond, F. L. Weitl, P. W. Durbin, *J. Med. Chem. 24* (1981) 203; K. N. Raymond, G. Müller, B. F. Matzanke, *Top. Curr. Chem. 123* (1984) 49.
[8] Elemental analyses and spectra are consistent with the synthesized compounds.
[9] I. G. O'Brien, G. B. Cox, F. Gibson, *Biochim. Biophys. Acta 237* (1971) 537.
[10] F. Vögtle, G. Hohner, *Angew. Chem. 87* (1975) 522; *Angew. Chem. Int. Ed. Engl. 14* (1975) 497; G. Hohner, F. Vögtle, *Chem. Ber. 110* (1977) 3052; S. Karbach, F. Vögtle, *ibid. 115* (1982) 427.

Synthesis and Crystal Structure of $[Ph_4As]_4[Au_{12}S_8]$, a Distorted Cubane-Like Thioaurate(I)**

By *Gerolf Marbach* and *Joachim Strähle**

In aqueous solutions of polysulfides, gold salts form thio- or polysulfidoaurates(I); the thioaurates(I) $[AuS]^{\ominus}$ and $[AuS_2]^{3\ominus}$ as well as the trisulfidoaurate(I) $[AuS_3]^{\ominus}$ were reported in the older literature[1]. Recently, we reported the synthesis and structure of $[Ph_4As][AuS_9]$, a cyclic nonasulfidoaurate(I)[2]. This species is formed from ethanolic solutions of $K[Au(SCN)_2]$ and tetraphenylarsonium polysulfide. Depending on the sulfur content of the polysulfide solution, salts of the cyclic anion $[Au_2S_8]^{2\ominus}$ are also obtained[3,4]. Thioaurates should be important for the chemical sensitization of photographic silver halide layers[5], in which $Ag[AuS]$[6,7] and $Ag_3[AuS_2]$[7] may occur. We have now obtained the thioaurate(I) $[Ph_4As]_4[Au_{12}S_8]$ **1**.

The gold sulfides Au_2S and Au_2S_3 as well as tetrachloroaurates(III) can be dissolved in concentrated aqueous solutions of Na_2S; presumably, thioaurate(I) ions $[AuS_2]^{3\ominus}$ are predominantly formed, whereby the Au^{III} compounds are reduced. Upon addition of Ph_4AsCl, **1** precipitates quantitatively from these solutions as light yellow crystalline needles[8].

1 forms intensely yellow solutions in dimethylformamide and dimethyl sulfoxide; columnular single crystals of **1** precipitate out from dimethyl sulfoxide when the solution slowly takes up H_2O from exposure to an atmosphere of water vapor. **1** is light sensitive and upon irradiation decomposes with a dark coloration. Decomposition also occurs at the melting point (230°C). In the mass spectrum, only fragments of the cation can be detected. Apart from the shoulder for ν(Au–S) at 330 cm^{-1}, the IR spectrum exhibits only the characteristic bands of the cation. The X-ray structure investigations were carried out at −60°C[9]. Compound **1** is isotypic with the thiocuprate(I) $[Ph_4P]_4[Cu_{12}S_8]$[10].

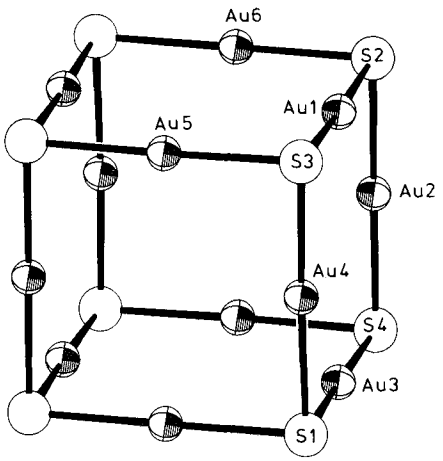

Fig. 1. Structure of the thioaurate(I) $[Au_{12}S_8]^{4\ominus}$ in the crystal of **1**. For clarity, the Au and S atoms are each represented by circles of the same diameter. Selected distances [pm] and angles [°]: Au-S 223.7(5)–234.6(5); Au-Au 317.9(1)–335.1(1), S-Au-S 177.8(2)–179.4(2), Au-S-Au 86.7(2)–93.1(2).

In the crystal, the anion of **1**, $[Au_{12}S_8]^{4\ominus}$, adopts a distorted cubic structure whose corners and edge midpoints are occupied by sulfur and gold atoms, respectively (Fig. 1). Gold(I) thus achieves its preferred linear coordination with bond angles S-Au-S between 177.8 and 179.4°. The average distance Au-S (230.6 pm) suggests a covalent single bond; the S atoms each bridge three Au atoms and enclose Au-S-Au angles of between 86.7 and 93.1°. A comparable arrangement occurs in the complex ion $[S(AuPPh_3)_3]^{\oplus}$ (Au-S: 230.2–234.2 pm, Au-S-Au 82.9–95.0°)[11].

In the anion $[Au_{12}S_8]^{4\ominus}$, the Au atoms are arranged cluster-like in the form of an almost ideal cuboctahedron. The Au-Au distances are between 318 and 335 pm. No Au-Au or Au-S contacts occur between the individual anions. In contrast to **1**, in the analogous thiocuprate $[Ph_4P]_4[Cu_{12}S_8]$[10] the Cu atoms are displaced towards the center of the cuboctahedron. Accordingly, the shorter Cu-Cu distances give rise to a marked bending of the S-Cu-S moiety.

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[8] *Procedure:* Au_2S (426 mg, 1 mmol) is dissolved in excess of an aqueous solution of Na_2S (ca. 0.4 M) at 70–90 °C. After removal of the residue by filtration, a solution of Ph_4AsCl (315 mg, 0.75 mmol) in 40 mL H_2O is added to the clear yellow solution. Immediately, a bright yellow, crystalline precipitate of **1** is formed, which is filtered off, washed twice with water, and dried in vacuo. The yield is quantitative.
[9] **1** forms monoclinic crystals, space group $P2_1/n$, $a=1428(2)$, $b=2640(2)$, $c=1300(2)$ pm, $\beta=91.5(1)°$, $Z=2$, $R=0.063$ for 1600 symmetry-independent reflections (ENRAF-NONIUS, CAD4; $Mo_{K\alpha}$). Further details of the crystal structure analysis can be obtained from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen, by quoting the depository number CSD 50914, the names of the authors, and the journal citation.
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2-(Pyridyl)ethyl Esters as Secure yet Readily Removable Polarophilic Carboxy-Protection in Peptide Synthesis**

By *Horst Kunz** and *Michael Kneip*

Dedicated to Professor Jan Thesing on the occasion of his 60th birthday

For the synthesis of sensitive peptides and glycopeptides, we have developed protective groups which are introduced in a stable form and only converted into a labile form immediately prior to their cleavage[1]. Among these two-step protecting groups, the 2-(pyridyl)ethoxycarbonyl (Pyoc) residues[2,3], both of which are stable to acids and bases, show the additional effect of increasing the solubility of the blocked amino acids and peptides in polar media. After methylation to the pyridinium form, they can be removed from the blocked amino group even with morpholine in dichloromethane.

To extend exploitation of the advantages of this protecting principle to the carboxy function, we have synthesized amino acid-2-(2-pyridyl)ethyl (2-Pet)[4] and amino acid-2-(4-pyridyl)ethyl (4-Pet) esters and checked their suitability for use in peptide synthesis. Because of their Lewis-base character, 2-(pyridyl)ethanols **3** and **4**[5] cannot be esterified directly with amino acids. In contrast, both benzyloxycarbonyl- **1** as well as *tert*-butoxycarbonyl-amino acids **2** react with dicyclohexylcarbodiimide (DCC)/4-dimethylaminopyridine (DMAP)[6] and **3** or **4** to give the *N*-protected amino acid-Pet esters **5**—**7**[7] in high yields (Scheme 1, Table 1).

With exception of **5a** (m.p. 67 °C) and **5g** (m.p. 76 °C), the 2-Pet esters are oily. The 2-Pet esters show, as characteristic ^{1}H-NMR signals ($CDCl_3$), two triplets ($\delta=3.15$ and 4.5, $J=6$ Hz) of the ethylene protons as well as a multiplet ($\delta=7.3$) and a doublet ($\delta=8.4$, $J=6$ Hz, α-H) of the pyridyl protons, while the latter give rise to doublets ($\delta=8.4$ and 7.15) in the spectra of the 4-isomer **7**.

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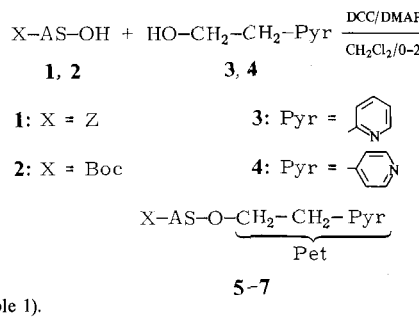


Scheme 1 (see Table 1).

Table 1. Synthesis of *N*-protected amino acid-(2-Pet) esters **5**, **6** and amino acid-(4-Pet) esters **7** according to Scheme 1.

	AA	X	Yield [%]	$[\alpha]_D^{22}$	(*c* in $CHCl_3$)
5a	Gly	Z	87	–	
5b	Ala	Z	88	– 3.5	(0.8)
5c	Val	Z	90	+ 2.8	(1.9)
5d	Leu	Z	92	– 6.2	(2.2)
5e	Ile	Z	81	+ 7.5	(2.1)
5f	Phe	Z	90	+23.5	(1.9)
5g	Ser [8]	Z	61	–43.4	(1.5)
6a	Leu	Boc	86	– 7.9	(2.0)
6b	Val	Boc	94	+ 2.8	(1.8)
7a	Val	Z	83	+ 2.5	(1.9)
7b	Phe	Z	90	+23.5	(2.1)

The peptide synthesis reactions were carried out with the derivatives **5**, **6** of the commercially available 2-isomer **3**. The hydrogenolysis of the Z-group in the compounds **5** takes place slowly. In contrast, the acidolysis of the two amino-protecting groups proceeds selectively and in high yields (Scheme 2).

5 $\xrightarrow{HBr/AcOH}$ H-AA-O-(2-Pet)·2 HBr
8a: AA = Val, 88%
8b: AA = Phe, 92%
8c: AA = Ile, 89%

6a $\xrightarrow{HCl/CH_2Cl_2}$ H-Leu-O-(2-Pet)·2 HCl
8d, 92%

Scheme 2.

The amino acid-Pet esters are formed as analytically pure dihydrohalides (elemental analysis). The dihydro salt is likewise formed on cleavage of Boc with trifluoroacetic acid. For the peptide coupling, the bases liberated from **8** are allowed to react with *N*-protected amino acids and ethyl-2-ethoxy-1,2-dihydroquinoline-1-carboxylate (EEDQ)[9] (**A**) or with dicyclohexylcarbodiimide (DCC)/1-hydroxybenzotriazole (HOBT)[10] (**B**) (Scheme 3, Table 2).

1, 2 + **8** $\xrightarrow[\substack{\mathbf{A}:\text{EEDQ}\\ \mathbf{B}:\text{DCC/HOBT}}]{2\,NEt_3/CH_2Cl_2}$ X-AA^1-AA^2-O-(2-Pet)
9: X = Z
10: X = Boc

Scheme 3 (see Table 2).

Once again, the amino protecting groups can be removed selectively from the analytically pure dipeptides **9** and **10** by acidolysis.

9f $\xrightarrow{HBr/AcOH}$ H-Leu-Phe-O-(2-Pet)·2 HBr
11a, 95%

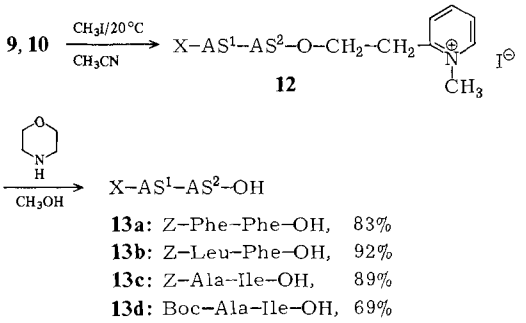
10a $\xrightarrow{HCl/CH_2Cl_2}$ H-Val-Leu-O-(2-Pet)·2 HCl
11b, 97%

10c $\xrightarrow{CF_3COOH}$ H-Gly-Leu-O-(2-Pet)·2 CF_3COOH
11c, 96%

Table 2. Synthesis of *N*-protected dipeptide-(2-Pet) esters according to Scheme 3.

	AA[1]	AA[2]	Yield [%] A	Yield [%] B	M.p. [°C]	$[\alpha]_D^{22}$ (c in $CHCl_3$)
9a	Ala	Phe	91	—	92–93	+13.3 (2.1)
9b	Gly	Phe	95	91	95	+29.0 (1.7)
9c	Phe	Phe	86	—	129	+21.8 (1.6)
9d	Phe	Ile	87	—	88–89	+ 7.3 (1.7)
9e	Leu	Ile	—	95	oil	− 6.5 (2.4)
9f	Leu	Phe	78	—	100	+ 8.6 (1.3)
10a	Val	Leu	—	88	66–68	−17.8 (1.5)
10b	Ala	Ile	76	—	oil	−18.4 (1.0)
10c	Gly	Leu	—	75	oil	+ 1.8 (2.1)

By analogy to the *N*-terminal Pyoc protecting groups[3], the Pet esters are activated by methylation in acetonitrile prior to cleavage (Scheme 4).



Scheme 4.

At room temperature, the methylation of the 2-Pet ester requires ca. 4 d. As a rule the isolable and characterizable pyridinium salts **12** are decomposed directly with 15% morpholine in methanol at room temperature in a E1cB reaction, which is complete after 2 h.

Methylation of the 4-Pet esters under the same conditions requires only 3 h. It was demonstrated with phenylalanine as example that the introduction and removal of the two isomeric Pet-esters proceeds almost without any racemization. Reaction of Z-Phe-OH **1f** ($[\alpha]_D^{22} = +4.6$ ($c = 2$, AcOH) with **3** or **4** yields, according to Scheme 1, the Pet-esters **5f** and **7b**, respectively, which can be cleaved again, according to Scheme 4, to give **1f** ($[\alpha]_D^{22} = 4.5$ ($c = 2$, AcOH)).

The Pet-esters are thus cleavable under mild conditions. Their polarophilic properties also enable an effective linking in the case of hindered hydrophobic building blocks.

13a + **8b** $\xrightarrow{\text{EEDQ}}$ Z-Phe-Phe-Phe-O-(2-Pet)
14a, 97%

13c + **8d** $\xrightarrow{\text{EEDQ}}$ Z-Ala-Ile-Leu-O-(2-Pet)
14b, 92%

The methylation necessary for the activation, however, precludes any application to sulfur-containing amino acids.

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[7] Procedure: A solution of **1** or **2** (10 mmol), **3** or **4** (1.2 g, 10 mmol) and DMAP (0.6 g, 0.5 mmol) in CH_2Cl_2 (30 mL) was treated at −20°C with 2.2 g (11 mmol) DCC. After 10 min the cooling bath was removed, the mixture was stirred for 3 h at 20°C, cooled to 0°C, and filtered free of dicyclohexylurea; the rest of this compound was then removed by dissolution in acetone at 0°C. The solution of the products **5**–**7** in 50 mL ether was washed with $NaHCO_3$ solution and water, dried over Na_2SO_4, and evaporated to dryness in vacuo. Filtration through a short silica gel column (20–30 g silica gel, eluent: chloroform) furnished analytically pure products.
[8] In contrast to [7], **3** was used here in tenfold excess. After completion of the reaction, the mixture was filtered and the product isolated directly by flash chromatography on silica gel (eluent: petroleum ether/ethyl acetate 1:20).
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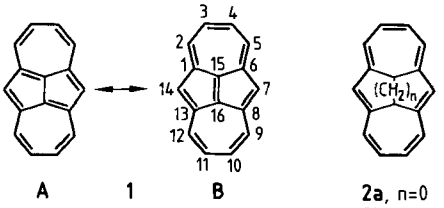
Novel Synthesis and Molecular Structure of the Pyrene Isomer Dicyclohepta[*cd,gh*]pentalene (Azuleno[2,1,8-*ija*]azulene)

By *Emanuel Vogel**, *Herbert Wieland*, *Lutz Schmalstieg*, and *Johann Lex*

Dedicated to Professor Virgil Boekelheide on the occasion of his 65th birthday

The pyrene isomer dicyclohepta[*cd,gh*]pentalene (azuleno[2,1,8-*ija*]azulene) **1**[1], according to the results of spectroscopic studies[2], can be viewed to a crude approximation as a 14π-Hückel perimeter with a central C=C bridge (large contribution from the numbered resonance structure). Thus, the relationship of **1** to the bridged [14]annulenes **2**[3] not only rests on a formal structural analogy, but also extends to the nature of the π-electron system. Previous attempts to perform an X-ray structure analysis of **1** failed because of the poor quality of the crystals and, hence, the alleged planarity of the molecule was not corroborated. Limited access to **1**, on the other hand, left unsettled the interesting question as to whether **1** might undergo additions to the central "double bond" to form **2a** or derivatives thereof. Both questions have recently become topical due to the surprising observation that 15,16-dioxo-*syn*-1,6:8,13-bismethano[14]annulene undergoes thermal deoxygenation—via a metathesis reaction sequence—to yield **1**[5].

The novel synthesis of **1** reported here (Scheme 1) now permits a more detailed investigation of the compound. The synthetic plan was based on the preparation of the α-chloro sulfoxide **8**, since we expected that this decisive intermediate could be directly converted into **1** via a Ramberg-Bäcklund-type rearrangement[6].



2a, n=0
2b, n=1
2c, n=2
2d, n=3

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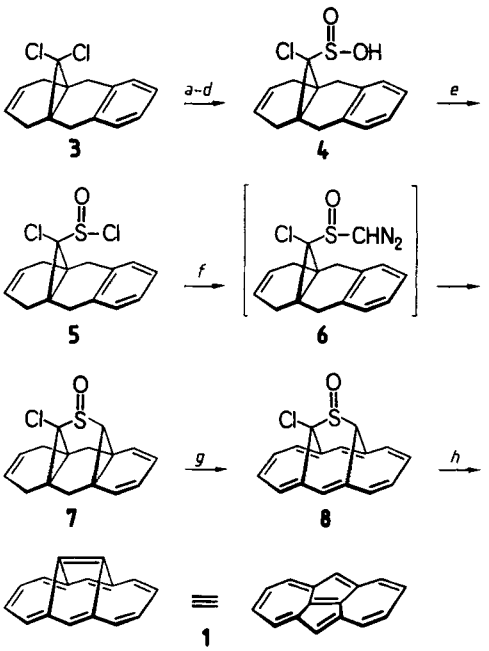

Scheme 1. *a:* *n*BuLi, THF (tetrahydrofuran) −78°C. *b:* SO_2 (gas), −78°C (until color changes from red to yellow). *c:* Cation exchange resin Lewatit S 100 as Na form, RT. *d:* H_2O/HCl; 59% (crude product) rel. to **3**. *e:* $SOCl_2$, THF (with pyridine) RT, 30 min. *f:* **5** (in THF) treated with CH_2N_2/ether, −70°C up to RT, 2 h; 28–33% rel. to **4**. *g:* 2,3-dichloro-5,6-dicyano-*p*-benzoquinone, chlorobenzene, 140°C, 3 h; 60%. *h:* KO*t*Bu, THF, −78°C up to RT, 1 h; 95%.

1,4,9,10-Tetrahydroanthracene, readily accessible by Birch reduction of 9,10-dihydroanthracene[7], selectively takes up dichlorocarbene at the tetrasubstituted double bond when allowed to react with chloroform and 25% aqueous potassium hydroxide in the presence of benzyltriethylammonium chloride (Makosza method) to afford adduct **3**, which is isolated by high-vacuum distillation (removal of nonvolatile bis-adduct) and crystallization from toluene (m.p. = 107°C; yield 40%). The dichloro compound **3** (Table 1) proved to be more suitable than the analogous dibromide used previously for the synthesis of bridged [14]annulenes, since lithiation of **3** proceeds with higher *endo*-selectivity than that of the dibromide (>90% compared to ca. 75%), as inferred from the protonation and carboxylation of the anion formed. Successive treatment of **3** with butyllithium and sulfur dioxide yields the lithium salt of the sulfinic acid **4** [or the stereoisomer of **4**] (Table 1), which is converted into the readily isolable crystalline sodium salt. If an aqueous solution of the sodium salt at 0°C is treated with concentrated hydrochloric acid, and the amorphous product thus precipitated taken up in ether, the practically pure microcrystalline *endo*-sulfinic acid **4**, which requires no additional purification [a sample recrystallized from ether melted at 139–141°C (decomp.)], is obtained after removal of the solvent. A solution of the acid chloride **5** in THF, prepared from **4** by treatment with sulfinyl chloride in THF, was allowed to react with excess diazomethane to furnish the diazo sulfoxide **6**. Since diazo sulfoxides have a strong tendency to decompose into carbenes[8], it was feasible that **6** might react further in statu nascendi to yield **7**. In fact, **7** is the major, readily separable product obtained upon chromatographic filtration through aluminum oxide (THF) [m.p. = 219–221°C (decomp.), colorless crystals from dioxane; see Table 1]. **7** can be straightforwardly dehydrogenated to **8** [m.p. = 240°C (decomp.), orange needles from dioxane; see Table 1].

Table 1. Spectral data for **3**, **4**, **7**, and **8**. ^{1}H-NMR (90 MHz, $CDCl_3$); MS (70 eV).

3: ^{1}H-NMR: δ = 2.10–2.75 (m, 4H), 2.95 (s, 4H), 5.5 (s, 2H), 7.15 (s, 4H); MS: *m/z* 264/266 ($M^{\oplus}$, 8/5%), 229/231 ($M^{\oplus}$ − Cl, 12/4), 193 ($M^{\oplus}$ − 2Cl, 57), 116 (100)

4: ^{1}H-NMR: δ = 2.10–2.75 (m, 4H), 3.17 and 3.34 (AB system, 2×2H), 5.60 (s, 2H), 7.00 (s, 1H), 7.00–7.25 (AA'BB' system, 4H); MS: *m/z* 294/296 ($M^{\oplus}$, <1%), 240 ($M^{\oplus}$ − H_2O − HCl, 8), 178 (100); IR (KBr): 2900, 2460 cm^{-1} (O–H), 1095 (S=O), 830 (S–O)

7: ^{1}H-NMR: δ = 1.67 (s, 1H), 2.05–3.53 (m, 8H), 5.60 (s, 2H), 5.75–6.20 (ABCD system, 4H); MS: *m/z* 290/292 ($M^{\oplus}$, 6/2%), 273 ($M^{\oplus}$ − OH, 25), 255 ($M^{\oplus}$ − Cl, 5), 237 ($M^{\oplus}$ − H_2O − Cl, 18), 165 (100); UV/VIS (dioxane): λ_{max} = 225 nm (ε = 2840) sh, 258 (2920), 280 (1780) sh; IR (KBr): 1064 cm^{-1} (S=O)

8: ^{1}H-NMR: δ = 0.20 (s, 1H), 7.45–8.10 (m, 8H), 7.95 (s, 1H), 8.35 (s, 1H); MS: *m/z* 286/288 ($M^{\oplus}$, 18/8%), 235 ($M^{\oplus}$ − O − Cl, 5), 234 ($M^{\oplus}$ − OH − Cl, 5), 203 ($M^{\oplus}$ − SO − Cl, 100); UV/VIS (dioxane): λ_{max} = 237 nm (ε = 5200), 303 (111000), 356 (5350), 437 (110) sh, 503 (330); IR (CsI): 1079 cm^{-1} (S=O)

The expectation that the α-chloro sulfone can be omitted as intermediate in the conversion of **8** into **1** proved to be correct. The α-chloro sulfoxide **8** gives **1**[13], almost quantitatively, which crystallizes from cyclohexane as greenish black needles (m.p. = 142°C); the spectral data of the compound agree with those reported previously[2].

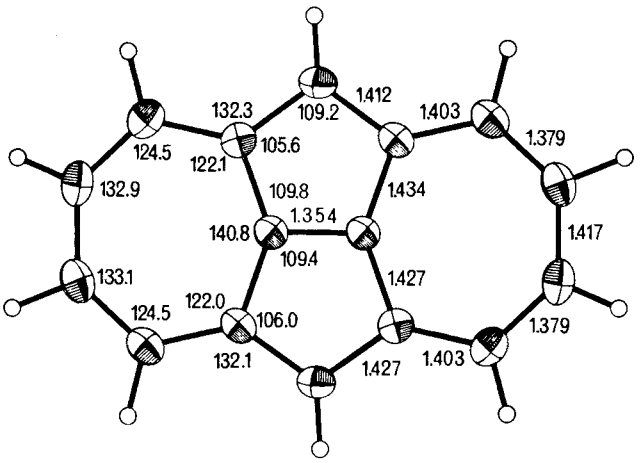

Fig. 1. Structure of **1** in the crystal. The bond lengths [Å] and bond angles [°], respectively, are shown in the right and left halves of the centrosymmetric molecules.

It was now found to be possible to carry out an X-ray structure investigation of **1** (see Fig. 1)[9]. The principal result is the verification of the assumed planarity of the molecular framework (maximum deviation of the C atoms from the mean plane through the ring skeleton: 0.013 Å). The molecule has a center of inversion and, within the limits of error, D_{2h} symmetry. The C_{14}-perimeter exhibits CC bonds of length 1.379 to 1.427 Å, which closely correspond to the respective bond distances in the peripheral annulene ring of the bridged aromatic [14]annulenes **2a** and **2b**[10]. The central bond C15–C16 is conspicuously short. This result suggests a relatively strong π-bond character for this bond, even when it is taken into account that a certain compression of the C15–C16 distance is brought about by the ring strain in **1**[10]. The concept that **1** is a [14]annulene perturbed by a central C=C bridge is thus supported not only by the spectral but also by the structural findings[11, 12]

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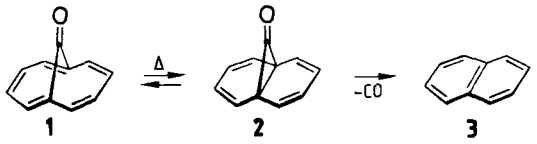
Thermal Deoxygenation of *syn*-15,16-Dioxo-1,6:8,13-bismethano[14]annulene to the Pyrene Isomer Dicyclohepta[*cd,gh*]pentalene (Azuleno[2,1,8-*ija*]azulene)

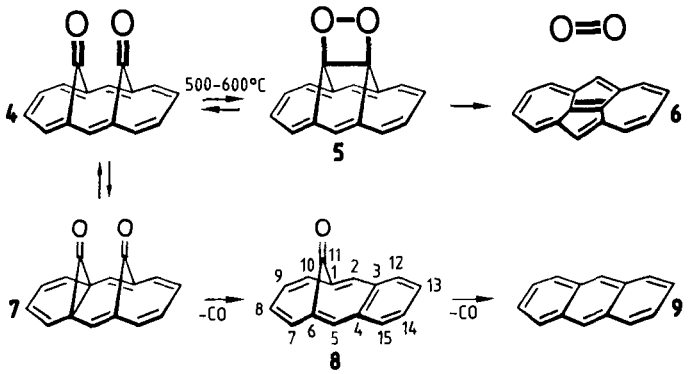
By *Emanuel Vogel*, Gerd Markowitz, Lutz Schmalstieg, Shô Itô, Rolf Breuckmann,* and *Wolfgang R. Roth*

The 10π-arene 11-oxo-1,6-methano[10]annulene **1**[1] is stable up to ca. 200°C. Above this temperature, it undergoes quantitative decarbonylation to yield naphthalene **3**, a reaction which in the gas phase is found to have the activation parameters $E_a=35.6\pm0.1$ kcal/mol and $A=(7.2\pm0.7)\times10^{13}$ s^{-1}. The relatively high thermal stability of **1**[2] can be rationalized if one assumes that the decarbonylation of the "masked tropone" **1** occurs via its energy-rich norcaradienone valence tautomer **2**. In view of the lack of knowledge on the properties of norcaradienones[3], it is an open question whether the formation or decomposition of **2** is rate determining.



The thermolysis behavior of **1** suggests that the most probable thermolytic reaction of the aromatic *syn*-15,16-dioxo-1,6:8,13-bismethano[14]annulene **4**[1c] would be fragmentation via the norcaradienone **7** to anthracene **9** and carbon monoxide. **4** should even exceed **1** in thermal stability since the formation of **7** is without doubt energetically more costly than that of **2**, because a) loss of resonance energy on going to the respective norcaradienone intermediate is greater for **4** than for **1** and b) increase of the annulene perimeter from ten to fourteen carbon atoms is associated with reduction of ring strain (the bridgehead angle of **1** is 106.1°[1d] as compared to 112.4°[4] in **4**). In fact, **4** is unexpectedly stable for a molecule of this structural type. As indicated by preliminary studies, **4** survives gas-phase pyrolysis at 500°C in vacuo virtually unscathed[5].

A more detailed investigation has now revealed that between 500 and 600°C **4** is deoxygenated to 70% to give the pyrene isomer dicyclohepta[*cd,gh*]pentalene **6**[6] (azuleno[2,1,8-*ija*]azulene), whereas decarbonylation to anthracene and carbon monoxide, which was anticipated to be the favored decomposition mode, only occurs to 30%. **6** was identified by comparison of its mass, NMR, and UV/VIS spectra with those of an authentic sample[6b].



Thermal deoxygenation of **4** to **6** can hardly be explained unless it is assumed that the 1,2-dioxetane **5** is formed initially; this then decomposes into **6** and singlet oxygen (as yet undetected), a reaction which competes with re-formation of **4**. To the best of our knowledge, there is no precedence for a metathesis reaction sequence of this type—reversal of the thoroughly studied oxidative cleavage of electron-rich double bonds by singlet oxygen[7]. That **4** proves to be a suitable substrate for the observation of such a reaction sequence must have its origins in the interplay of the following factors:

1) The rigid, approximately parallel arrangement of the carbonyl groups in **4** appears to make a 1,2-dioxetane ring closure favorable for entropy reasons.

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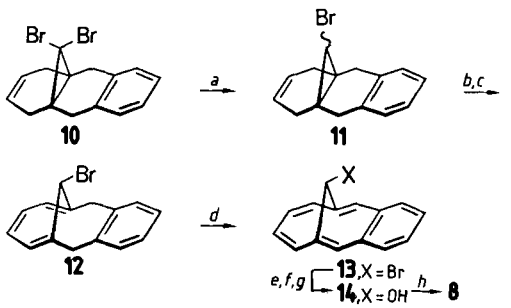
2) The reaction conditions (flow thermolysis) permit kinetic control of the products, thereby fulfilling an important requirement for the realization of the strongly endothermic 1,2-dioxetane formation.
3) The pyrolysis temperature of 500—600 °C is sufficient to reach the high activation threshold[8] expected for establishment of the equilibrium **4** ⇄ **5**.
4) Liberation of singlet oxygen from **5** should benefit from formation of an aromatic product[9]. **6** is planar[6b] and, so corresponding to its enthalpy of hydrogenation ($\Delta H = -165.2$ kcal/mol), has a high resonance energy.

Apart from **4**, the majority of other known diketones with neighboring, parallely orientated carbonyl groups are cage compounds[10]. Thermal cleavage in the sense of the metathesis reaction sequence **4** → **5** → **6** is not possible in such diketones since extremely strained olefins would result.

The decarbonylation of **4** to **9**, which competes with the deoxygenation, proceeds in all probability via **8**. In order to corroborate this supposition experimentally, **8** was synthesized independently (Scheme 1) and its thermal behavior studied.



Scheme 1. *a*: Tri-*n*-butyltin hydride, toluene, reflux, 24 h; 95% (crude product). *b*: Br_2/CH_2Cl_2, −78 °C. *c*: DBN in THF (tetrahydrofuran), RT, 4d; 20% rel. to **10**. *d*: 2,3-Dibromo-5,6-dicyano-*p*-benzoquinone, toluene, reflux, 15 h; 7%. *e*: *n*BuLi, THF, −78 °C. *f*: $B(OCH_3)_3$, −78 to 15 °C, 1 h. *g*: 5% NaOH/30% H_2O_2, −15 °C, 1 h; 26%. *h*: DMSO/CH_2Cl_2/$(CF_3CO)_2O$, −78 °C, 1 h; 59%.

Reduction of the known dibromo compound **10** afforded the monobromide **11** as a mixture of the *exo/endo*-isomers (ca. 1 : 1.7). Attempts to isolate *endo*-**11** were unsatisfactory; however, after carrying out a bromination-dehydrobromination reaction sequence, product separation presented no difficulties. The *endo/exo*-**11** isomers readily took up bromine to form the tribromides. Treatment of this mixture with 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) resulted in dehydrobromination of the *endo*-isomer to **12**, whereas, in contrast, the *exo*-isomer remained intact. Extraction of the reaction mixture with methanol (room temperature) and subsequent chromatography on silica gel (pentane) led to pure **12** [m.p. = 56—57 °C (from methanol), see Table 1], which could be dehydrogenated to **13** [m.p. = 173—174 °C (from methanol), see Table 1] albeit in low yield[12]. Successive treatment of the solvolytically rather inert bromide **13** with butyllithium, trimethyl borate, and alkaline hydrogen peroxide caused smooth Br/OH-exchange, leading to **14** [m.p. = 130—131 °C (from ether/pentane), see Table 1]. For the conversion of **14** into **8**, oxidation with dimethyl sulfoxide/trifluoroacetic anhydride proved to be the method of choice; yellow needles of **8** [m.p. = 206—207 °C (decomp.)] were obtained after chromatography on silica gel and crystallization from ether (Table 1).

Table 1. Spectral data for **8**, **12**, **13**, and **14**. ^{1}H-NMR (90 MHz); MS (70 eV); UV/VIS (CH_2Cl_2); IR (KBr).

8: ^{1}H-NMR [$(CD_3)_2CO$]: $\delta = 6.86$ and 7.45 (AA'XX' system, H-8,9 and H-7,10; $J_{7,8} = 10.81$, $J_{7,9} = 0.07$, $J_{7,10} = 1.03$, $J_{8,9} = 8.39$ Hz), 7.56 (s, H-2,5), 7.64 and 8.17 (AA'XX' system, H-13,14 and H-12,15; $J_{12,13} = 8.11$, $J_{12,14} = 1.36$, $J_{12,15} = 0.53$, $J_{13,14} = 7.03$ Hz); ^{13}C-NMR (20 MHz; $CDCl_3$): $\delta = 201.8$ (C-11), 136.4 (C-1,6), 134.8 (C-3,4), 127.5 and 126.6 (C-8,9,13,14), 131.7, 124.7 and 122.8 (C-2,5,7,10,12,15); MS: *m/z* 206 ($M^{\oplus}$, 2.5%), 178 ($M^{\oplus} - CO$, 100), 152 ($M^{\oplus} - C_4H_6$, 13); UV/VIS: $\lambda_{max} = 273$ nm ($\varepsilon = 75500$), 344 (5140); IR: 1743 cm^{-1} (C=O)

12: ^{1}H-NMR (CCl_4): $\delta = 3.13$ (s, 1H), 3.42 and 4.10 (AB system, 2 × 2H), 6.10 and 6.57 (AA'XX' system, 4H), 6.88—7.18 (AA'BB' system, 4H); MS: *m/z* 272/274 ($M^{\oplus}$, <1%), 193 ($M^{\oplus} - Br$, 81), 178 (55), 115 (100); UV/VIS: $\lambda_{max} = 245$ nm ($\varepsilon = 4360$) sh, 280 (1020) sh, 362 (29) sh, 385 (18) sh

13: ^{1}H-NMR (CCl_4): $\delta = 3.77$ (s, 1H), 6.50 and 7.30 (AA'XX' system, 4H), 7.33 (s, 2H), 7.53 and 8.00 (AA'XX' system, 4H); MS: *m/z* 270/272 ($M^{\oplus}$, <1%), 191 ($M^{\oplus} - Br$, 100), 178 (20), 165 (45); UV/VIS: $\lambda_{max} = 280$ nm ($\varepsilon = 58500$), 349 (4780)

14: ^{1}H-NMR (CCl_4): $\delta = -0.47$ (s, br., 1H), 3.20 (s, 1H), 6.50 und 7.27 (AA'XX' system, 4H), 7.35 (s, 2H), 7.50 and 8.05 (AA'XX' system, 4H); MS: *m/z* 208 ($M^{\oplus}$, 11%), 191 ($M^{\oplus} - OH$, 11), 179 (100), 178 (90); UV/VIS: $\lambda_{max} = 278$ nm ($\varepsilon = 75800$), 351 (5060); IR: 3470 cm^{-1} (O—H)

In both solution and in the solid state, 11-oxo-3,4-benzo-1,6-methano[10]annulene **8** is stable up to ca. 200 °C, which corresponds to the stability behavior of the parent compound **1**. At higher temperatures, **8** is quantitatively decarbonylated to **9**. Accordingly, the thermal behavior of **8** is consistent with its assumed occurrence as intermediate in the decarbonylation of **4**.

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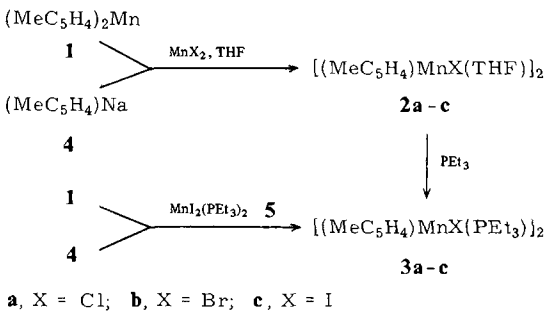
General Entry to Novel Manganese(II) Half-Sandwich Complexes**

By *Frank H. Köhler*, Nikolaus Hebendanz, Ulf Thewalt, Basil Kanellakopulos,* and *Reinhardt Klenze*

Numerous diamagnetic, and even some paramagnetic[1], transition-metal compounds with a π-bonded aromatic ligand (half-sandwich complexes) are effective functional groups for the stabilization of molecules and molecular fragments. Despite the reported involvement of "CpMnCl" intermediates in certain reactions[2], manganese(II) half-sandwich compounds of this type have hitherto never been isolated[3]. Herein, we report on the formation and properties of compounds of the type $CpMnXL_2$ and their dimers.

Bis(η-methylcyclopentadienyl)manganese **1** reacts with manganese(II) halides to give the compounds **2** (Scheme 1), in which the tetrahydrofuran (THF) ligand can be readily replaced by triethylphosphane. The complexes **3** thus formed can also be prepared by reaction of methylcyclopentadienylsodium **4** with the recently described bis(triethylphosphane)manganese diiodide **5**[4] (Scheme 1). **2a** and **3** are confirmed by elemental analysis. The complexes are very sensitive towards air and moisture.



Scheme 1.

According to an X-ray structure analysis[5], **3a** is dimeric, which also should be the case for **2** and **3b/3c**. Linkage by chloro bridges results in a tetrahedral environment of the Mn atoms (Fig. 1); the central Mn–Cl–Mn*–Cl* unit is almost square planar and thus, as in the case of $[CpCrCl_2]_2$[1g], **3a** can be expected to be antiferromagnetic. According to the ^{1}H-NMR spectrum (Fig. 2) and a cryoscopic determination of the molar mass of **3c** (790 ± 40, in benzene), the same type of structure is present in solution. The signals of the methylcyclopentadienyl protons are shifted similarly to the analogous signals in $(i\text{PrC}_5\text{H}_4)_2\text{Mn}$[6], thus indicating the presence (at 303 K) of ten unpaired electrons in the dimer. NMR spectroscopic investigations at various temperatures, however, show deviations from ideal paramagnetic behavior. More precise

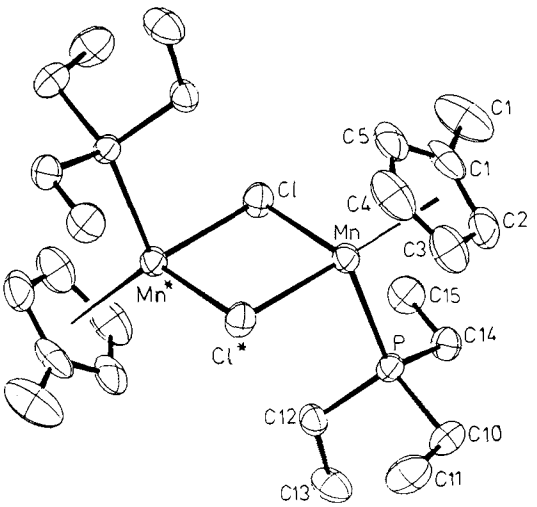


Fig. 1. Structure of **3a** in the crystal. Selected bond lengths [pm] and bond angles [°]: Mn-Cl 248.2(2), Mn-Cl* 248.0(2), Mn-P 256.7(2), Mn-Z 217.1(10), Mn-Mn* 351.4(2); Cl-Mn-Cl* 89.8, Cl-Mn-P 98.9, Cl*-Mn-P 99.3, Mn-Cl-Mn* 90.2. Z = center of the five-membered ring.

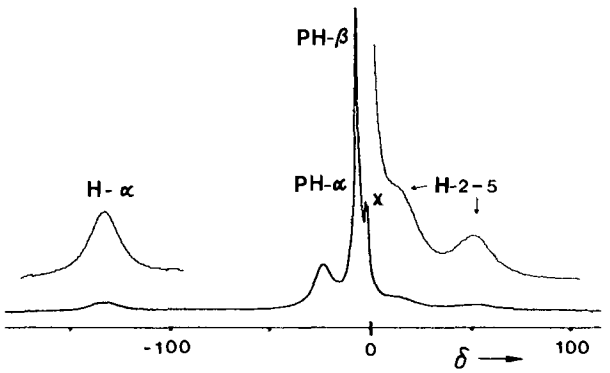


Fig. 2. 200-MHz ^{1}H-NMR spectrum of **3c** in $CD_3C_6D_5$ at 303 K. For assignment of signals cf. Figure 1: H-α ≙ H-1', PH-α ≙ H-10/12/14, PH-β ≙ H-11/13/15. X = residual methyl-H of the solvent and free PEt_3.

information is provided by the measurement of the magnetic susceptibility of **3a** (crystal powder) between 1.3 and 332.9 K (Fig. 3): **3a** couples antiferromagnetically via Cl bridges. Referred to a magnetically normal complex, the data can be interpreted in terms of a coupling constant $J = -4.7\ \text{cm}^{-1}$ over the whole temperature range.

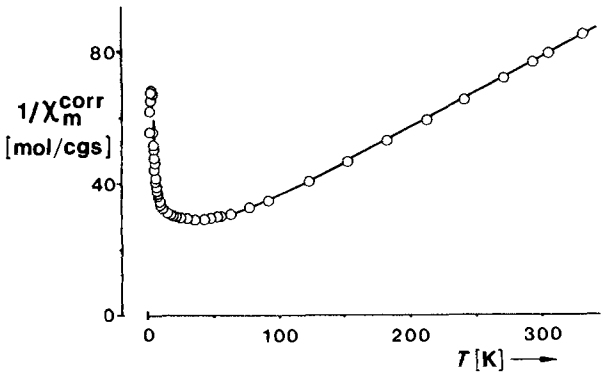


Fig. 3. Inverse molar magnetic susceptibility between 1.3 and 332.9 K.

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On reaction of **2c** with trimethylphosphane, we did not isolate dimers such as **3**, but the species **6** (confirmed by elemental analysis).

$$\underset{\mathbf{2c}}{[(MeC_5H_4)MnI(THF)]_2} \xrightarrow{PMe_3} 2\underset{\mathbf{6}}{(MeC_5H_4)MnI(PMe_3)_2}$$

Complex **6** differs characteristically in the paramagnetic shifts δ^{para} (^{1}H)[7] of its phosphane ligands from **3a**–**c**, which themselves exhibit very similar δ^{para} (^{1}H) values. In the PEt_3 derivatives **3**, coordinative saturation is achieved by dimerization, whereas the sterically undemanding PMe_3[8] moiety in **6** enables formation of the monomer. **6** is thus a particularly simple example of a manganese(II) half-sandwich complex.

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TMEDA Adducts of CpMnCl and Manganocene**

By *Jürgen Heck**, *Werner Massa*, and *Peter Weinig*

Cyclopentadienyl halogeno complexes of 4th, 5th and 6th sub-group elements have interesting magnetic properties and are of great preparative importance because of their reactive halogeno groups and their Lewis acidity[1]. We have now prepared and isolated, in a very simple reaction, the base-stabilized cyclopentadienylmanganese(II) chloride, whose methyl derivative $(CH_3C_5H_4)MnCl$ was reported as long ago as 1957 to be an intermediate in the synthesis of $(CH_3C_5H_4)Mn(C_6H_6)$[2]. Since monomeric cyclopentadienyl halogeno complexes $CpMCl_2$ (M = Ti, V, Cr; Cp = cyclopentadienyl) containing 11–13 valence electrons are obviously not isolable without Lewis bases under normal conditions[1] we resorted to the reaction of equimolar amounts of anhydrous $MnCl_2$, *N,N,N',N'*-tetramethylethylenediamine (TMEDA), and NaCp in tetrahydrofuran (THF). In this way, the air- and moisture-sensitive complex CpMn(TMEDA)Cl **1** was formed in very good yields[3,4] [Reaction (a)].

$$MnCl_2 + TMEDA \xrightarrow[\text{2. NaCp, 220 K}]{\text{1. THF, reflux}} \underset{\mathbf{1}}{CpMn(TMEDA)Cl} + NaCl \quad (a)$$

On attempting to split TMEDA by heating in a high vacuum, CpMnCl was not formed, but **2** as sublimate [Reaction (b)].

$$2\,\mathbf{1} \xrightarrow[390-410\ K]{10^{-3}-10^{-4}\ mbar} \underset{\mathbf{2}}{Cp_2Mn(TMEDA)} + MnCl_2 + TMEDA \quad (b)$$

2 is formed in almost quantitative yield on reaction of manganocene **3** with TMEDA in toluene[5] [Reaction (c)].

$$\underset{\mathbf{3}}{MnCp_2} + TMEDA \xrightarrow[290\ K,\ 2\ d]{toluene} \mathbf{2} \quad (c)$$

Magnetic measurements by NMR methods in solution[6] and ESR investigations[7] showed **1** and **2** to be high-spin complexes.

As in the case of **3**, the Cp signal in the ^{1}H-NMR spectra of **1** is found at higher field than the methyl signal of toluene[9], whereas the signals of the TMEDA ligands in **1** and **2** are shifted downfield (Fig. 1). Because of the paramagnetism of **1** and **2** ($S=5/2$) the δ^{para} values show characteristic temperature dependencies (Fig. 1)[10].

According to an X-ray structure analysis, Mn in **2** forms an η^5- as well as an η^1-bond to the Cp rings (Fig. 2); there is no tilted sandwich structure with two η^5-bonded Cp rings as in the pyridine adduct of the propano-bridged manganocene[11]. The average distance of the central metal from the C-atom of the η^5-Cp ring (250.7 pm, Table 1) is consistent with an ionic bonding[11a]. Surprisingly, the η^1-bonded Cp-ring shows no bond alternation[12] (Table 1), but similar CC bond lengths as in the Cp-ring of the ionic species Na(TMEDA)Cp[13]. Besides the relatively small angle between the Mn–C11 bond and the C11–C15 plane

Table 1. Important bond lengths [pm] and angles [°] in Cp_2Mn (TMEDA) **2**. Z = centroid of the η^5-Cp ring C21–C25.

Mn–C11	232.0(5)	Mn–C21	256.6(6)	Z–Mn–C11	131.9
Mn–C12	283.2(5)	Mn–C22	252.7(6)	Z–Mn–N1	116.8
Mn–C13	348.7(5)	Mn–C23	245.7(6)	Z–Mn–N2	118.0
Mn–C14	350.0(6)	Mn–C24	244.3(7)	C11–Mn–N1	97.9
Mn–C15	284.6(5)	Mn–C25	254.0(8)	C11–Mn–N2	99.9
mean	299.7	mean	250.7	N1–Mn–N2	78.6
		Mn–Z	222.3	mean	107.2
Mn–N1	233.8(5)	Mn–N2	235.4(5)		
C11–C12	139.8(8)	C21–C22	135.2(10)		
C12–C13	137.9(9)	C22–C23	133.9(9)		
C13–C14	137.1(9)	C23–C24	134.2(10)		
C14–C15	137.7(9)	C24–C25	138.5(12)		
C15–C11	141.5(9)	C25–C21	140.1(11)		
mean	138.8	mean	136.4		
(Mn–C11)–plane C11–C15		100.2	(Mn–Z)–plane C21–C25		93.6

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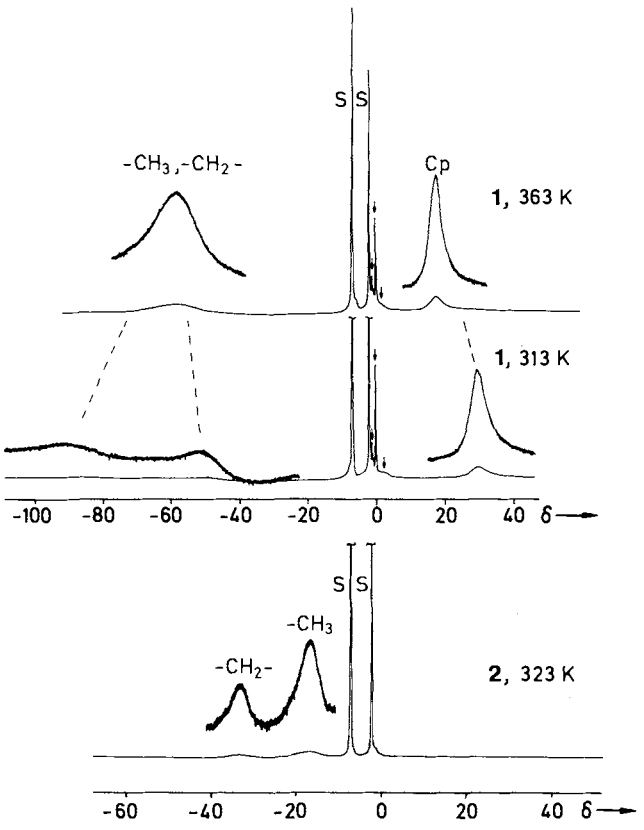

Fig. 1. 400-MHz ^{1}H-NMR spectra of **1** and **2** in [D$_8$]toluene (=S); ↓ impurities.

(100.2°, Table 1) and the angle between the plane C11–C15 and the C11–H bond (13°), a Mn–C11 distance markedly larger than that found for covalent Mn–C bonds is observed, which likewise indicates ionic character of the Mn-η^1-Cp bond. Hence, there are distinct similarities with a section of the chain structure of Cp_2Mn[14]. The two N-atoms of the TMEDA ligand occupy two further coordination sites on Mn[11], resulting in a strongly distorted tetrahedral structure in **2**. The ESR findings on rigid solutions of **2**[7] and the magnetic findings in solution are in agreement with this structure.

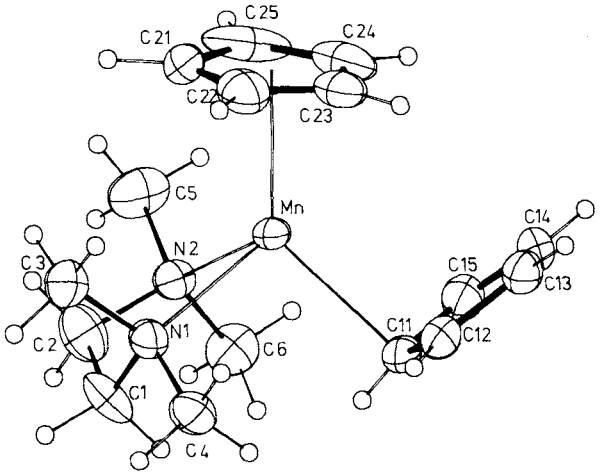

Fig. 2. Structure of Cp_2Mn(TMEDA) in the crystal (ORTEP diagram, thermal ellipsoids at the 30% probability level), Space group $P2_1/n$, $Z=4$, $a=1237.4(3)$, $b=969.4(1)$, $c=1342.3(1)$ pm, $\beta=101.24°$. $R_w=0.038$ (weighting $w=1/2\sigma^2(F_0)$ for 1445 independent reflections with $F_0>2\sigma$; CAD4, Enraf-Nonius, $Mo_{K\alpha}$ radiation). Important bond lengths and angles in Table 1. Maximum deviation of the C-atoms of the Cp rings from "best planes" 0.6 pm. Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD 50925, the names of the authors, and the journal citation.

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CAS Registry numbers:
1, 91742-12-0; **2**, 91742-13-1; **3**, 73138-26-8.

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[3] A stirred solution of anhydrous $MnCl_2$ (8.19 g, 65.1 mmol) and TMEDA (9.7 mL, 65.1 mmol) in THF (400 mL) was heated under reflux for 3 h in the absence of air and H_2O. After cooling to 220 K a solution of NaCp (5.13 g, 65.1 mmol) in THF (100 mL) was added dropwise and after 3 h the mixture was allowed to warm to room temperature, evaporated to dryness, and the residue extracted at 350 K with 500 mL toluene. After cooling to 250 K for 3 d, **1** could be isolated as bright green crystals (yield 15.3 g, 86%).

[4] Concomitantly, and independently, *Köhler* et al. have synthesized a dimeric methylcyclopentadienylmanganese(II) chloride stabilized with PEt_3; F. H. Köhler, N. Hebendanz, V. Thewalt, B. Kanellakopulos, R. Klenze, *Angew. Chem. 96* (1984) 697; *Angew. Chem. Int. Ed. Engl. 23* (1984) 721.

[5] The suspension of 5 mmol of **2** obtained according to Reaction (c) was extracted at 340 K with 250 mL toluene (yield: 94.6%). The almost colorless crystalline **2** decomposes to dark brown products in the presence of traces of air.

[6] D. F. Evans, *J. Chem. Soc. 1959*, 2003. Solvent: toluene. **1**: $\mu_{eff}^{corr}=5.9$; **2**: $\mu_{eff}^{corr}=5.5$ B.M.

[7] Solutions of **1** in toluene at 4 K give a strong ESR signal at $g=5.8$ with a ^{55}Mn-HFS and a line interval of 81–84 G as well as weak signals for $g>6$. At 115 K an intense signal appears for $g=2.02$ without HFS. The ESR spectrum of **2** at 115 K contains the characteristic signals of distorted tetrahedra of the type MnA_2B_2 [8]. In liquid solutions, ESR signals without HFS are observed for **1** and **2**: (**1**: $g_{iso}=2.001$; **2**: $g_{iso}=2.010$).

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[9] D. A. Levy, L. E. Orgel, *Mol. Phys. 3* (1960) 583.

[10] The Cp signals of **2** can not be observed, presumably because of too broad a line width. The line equations for the temperature dependence of the reduced shifts ϑ ($\vartheta=\delta^{para}$ (T/298)) of individual sorts of protons are: $\vartheta(Cp(\mathbf{1}))=-0.19T+89$ ($243\leq T\leq 363$); $\vartheta(CH_3(\mathbf{2}))=0.40T-147$, $\vartheta(CH_2(\mathbf{2}))=0.02T-43$ ($190\leq T\leq 363$).

[11] a) J. T. Weed, M. F. Rettig, R. M. Wing, *J. Am. Chem. Soc. 105* (1983) 6510; b) cf. C. G. Howard, G. S. Girolami, G. Wilkinson, M. Thornton-Pett, M. B. Hursthouse, *ibid. 106* (1984) 2033.

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Stereoselective Nucleophilic Acylation of Benzaldehyde with a Crotonaldehyde-d^1 Reagent**

By *Manfred Braun** and *Wilhelm Hild*

The addition of "umgepolt" carbonyl compounds ("d^1 synthons") such as **1** to aldehydes with formation of the

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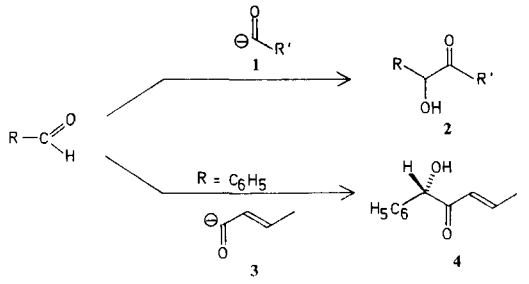
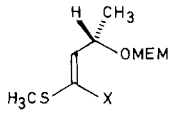
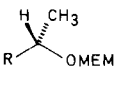
chiral acyloins **2** constitutes one of the most important C–C bond formations[1]; all attempts to synthesize **2** highly stereoselectively via lithiated sulfoxides[2a] or formamides[2b] have hitherto failed; the selectivity achieved is low[2b] or moderate[2a], and the reagents are in some cases difficultly accessible. We report here on the highly stereoselective addition of a crotonaldehyde-d^1 synthon **3** to benzaldehyde using the vinyllithium reagent **5a** obtained from (*S*)-lactic acid.



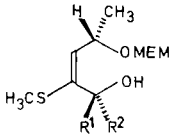
1 **2** **3** **4**



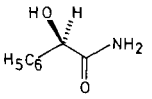
5a: X = Li
5b: X = H



6a: R = CHO
6b: R = C_2H_5



7a: R^1 = C_6H_5, R^2 = H
7b: R^1 = H, R^2 = C_6H_5



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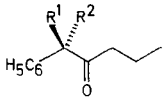
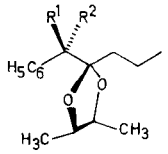


(*S*)-**9**: R^1 = H, R^2 = OH
(*R*)-**9**: R^1 = OH, R^2 = H



10a: R^1 = H, R^2 = OH
10b: R^1 = OH, R^2 = H

MEM = $CH_2OCH_2CH_2OCH_3$

Reduction of ethyl (*S*)-lactate with diisobutylaluminum hydride, after protection of the hydroxy group as (2-methoxyethoxy)methyl (MEM) ether, affords the aldehyde **6a**[3], which is converted by a Wittig-Horner reaction[4] into the vinyl sulfide **5b**. This reaction proceeds without racemization, as shown by a comparison of the optical rotations of the ether **6b**, obtained from **5b** by desulfuration with Raney nickel, and of the sample obtained from commercial (*R*)-2-butanol after introduction of the MEM protecting group. The (*Z*)-diastereomer of **5b** is not observed, not even in trace amounts thereof. Metalation of the vinyl sulfide **5b** with *n*-butyllithium in tetrahydrofuran (THF) affords the lithium reagent **5a** – as reprotonation shows, racemization-free; **5a** is then allowed to react in situ with benzaldehyde. The ratio of the diastereomers **7a** and **7b** thus formed in quantitative crude yield can be determined directly from the ^{1}H-NMR spectrum: on using THF/pentane as solvent it is 96 : 4[5]. Separation of the isomers could be achieved by layer chromatography, purification of the excess diastereomer **7a** by column chromatography on neutral aluminum oxide.

Treatment of the crude product **7a/7b** with mercury(II) chloride[6] in aqueous acetonitrile leads directly to the hydroxyenone **4**, whose absolute configuration and optical purity were proven as follows: On reaction of (*R*)-mandelic acid amide **8**[7a] with *n*-propylmagnesium bromide, (*R*)-**9** ($[\alpha]_{578} = -117°$, ethanol) is obtained. Since catalytic hydrogenation of the enone **4** affords the (+)-α-hydroxyketone **9** ($[\alpha]_{578} = +108°$, ethanol), this – and thus also the unsaturated ketone **4** – must be (*S*)-configurated. Hence, the structure **7a** can be assigned to the diastereomer formed in excess on addition of **5a** to benzaldehyde. The optical purity of (*S*)-**9** (92%) is consistent with the NMR spectroscopically determined diastereomeric ratio **7a** : **7b**. Since the occurrence of partial racemization in the reaction of the amide **8** with propylmagnesium bromide cannot, a priori, be ruled out with certainty[7b], the dioxolanes **10a** and **10b**, respectively, were prepared both from (*S*)-**9** as well as (*R*)-**9** by reaction with (*S,S*)-2,3-butanediol; **10a**, and **10b** differ markedly in their ^{1}H-NMR spectra. The acetal **10b** obtained from the amide **8** is free of **10a**, and the isomeric purity of **10a** prepared from **4a** via (*S*)-**9** is at least 95%.

A diastereomeric ratio 95 : 5 is likewise achieved on addition of **5a** to acetophenone. Since (*R*)-lactic acid is now readily obtainable by a biotechnological method[8] either of the two enantiomers of the enones of type **4** are easily accessible.

Experimental

(*S*)-**4**: A mixture of **5b** (0.90 g, 4.40 mmol) and THF (30 mL) was treated at –78 °C under an N_2-atmosphere with 3.9 mL of a 1.5 M solution of *n*-butyllithium in hexane. After 2 hours' stirring at –78 °C a solution of benzaldehyde (0.58 g, 0.55 mmol) in THF (10 mL) was added and the mixture stirred for a further 12 h at –78 °C. After the usual aqueous work-up, 1.37 g (ca. 100%) of the mixture **7a/7b** was obtained. This was dissolved in 40 mL acetonitrile and 20 mL water, treated with 2.42 g (8.9 mmol) $HgCl_2$ and heated under reflux for 1 h. After filtration and washing of the precipitate with ether, washing of the purified filtrate with $NaHCO_3$ solution, NaCl solution, and water, drying, removal of the solvent, and recrystallization of the residue from pentane there remained 0.45 g (57%) (*S*)-**4**. M.p. 54–56 °C ((±)-**4**: m.p. 56–57 °C [9]); the ^{1}H-NMR data are in good agreement with those given in the literature [9]; $[\alpha]_D = +271°$ ($c = 0.59$; $CHCl_3$).

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Synthetic Studies on the Elucidation of the Structure and Configuration of Dolastatin 3**

By *Ulrich Schmidt** and *Roland Utz*

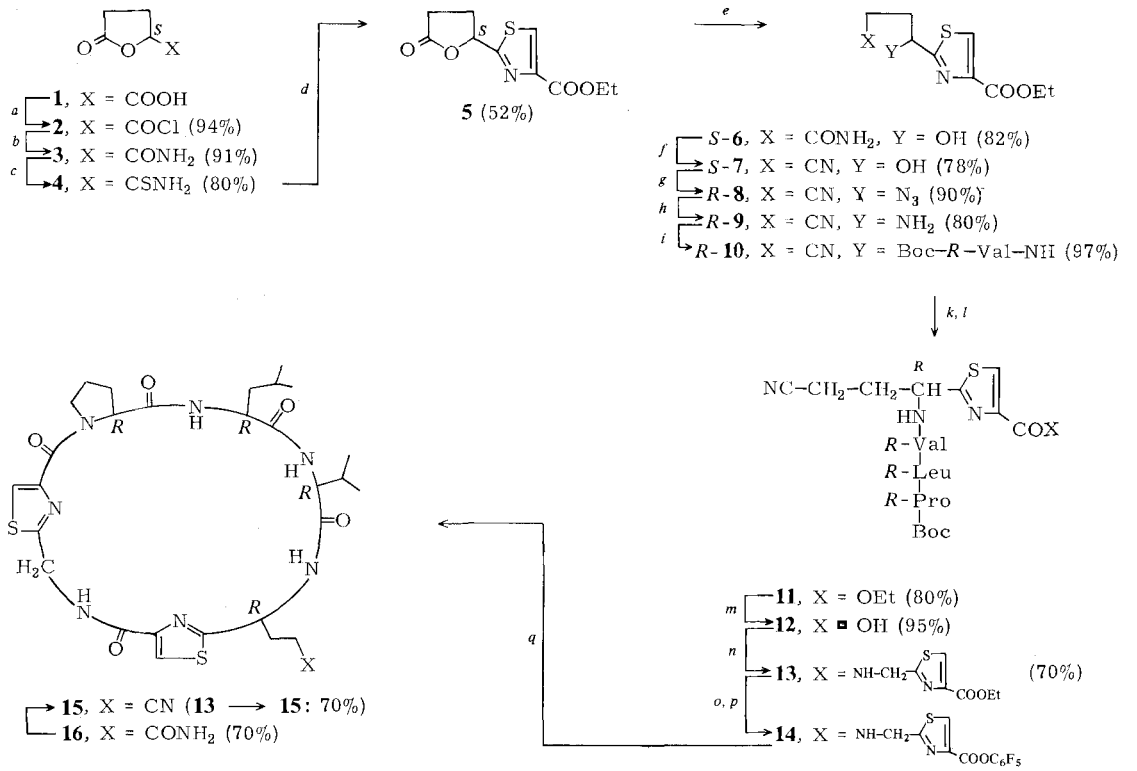
Dedicated to Professor Karl Schlögl on the occasion of his 60th birthday

Dolastatin 3, isolated from the Indian Ocean sea hare *Dolabella auricularia*, exhibits strong in vitro antineoplastic activity (P-388 leukemia cells: $ED_{50} = 1 \times 10^{-4}$ to 1×10^{-7} µg/mL). On the basis of the amino acid analysis and mass spectrum, *Pettit* et al.[1], who isolated ca. 1 mg of Dolastatin 3, proposed structure **16** for this compound, without determining its configuration. The (*S*)-configuration of the amino acids was presumed; the opposite "ring direction" (corresponding to **17**) was not ruled out, but was held to be less probable for biogenetic reasons.—Since the natural product is only accessible in small amounts, and with difficulty, its structure and configuration can only be elucidated by comparison with a synthetic product obtained by an unequivocal route.

Characteristic building blocks for the cyclopeptide are two 2-(aminoalkyl)-4-thiazolecarboxylic acids. Analogous compounds with (*R*)-configuration have been found in the cyclopeptides from other lower marine creatures by *Ireland* et al.[2]. Since racemic thiazole derivatives are obtained from thioamides of optically active α-acylamino acids[3], we employed α-acyloxy acids such as **1**, whose thioamides **4** afford optically active hydroxyalkylthiazolecarboxylates such as **6** and **7** with ethyl bromopyruvate (Scheme 1). This thiazole synthesis proceeds without racemization; thus, (1*S*,2*S*)-2-methyl-1-thiocarbamoylbutyl acetate ("(2*S*,3*S*)-2-acetoxy-3-methylvaleric acid thioamide") forms no diastereomeric thiazole with (1*R*,2*S*)-configurated side chain.

Mitsunobu reaction[4] of **7** leads to the azidoalkylthiazolecarboxylic acid ester **8**, which can be readily hydrogenated to the amino compound **9**. Since introduction of the azide functionality proceeds with inversion, but the optically active hydroxy acids (precursors of **1**) are formed from α-amino acids with retention of configuration, (*R*)-aminoalkylthiazolecarboxylic acid esters are obtained from natural (*S*)-amino acids. Ethyl (*R*)-2-(1-amino-3-cyanopropyl)-4-thiazolecarboxylate **9** is thus accessible from (*S*)-glutamic acid.

As shown in Scheme 1, **9** is allowed to react with an *R*-Val derivative to yield **10**, to which the dipeptide Boc-*R*-Pro-*R*-Leu is attached. The compound **11** thus obtained is coupled (after hydrolysis of the ethyl ester group) to ethyl 2-aminomethyl-4-thiazolecarboxylate to afford **13**. The pentafluorophenyl ester **14** prepared from this serves as a linear educt for the ring closure. After cleavage of the Boc group cyclization proceeds upon slow injection of the



Scheme 1. *a:* $SOCl_2$; *b:* NH_3; *c: Lawessons* reagent (2,4-bis(4-methoxyphenyl)-1,3-dithia-2λ⁵,4λ⁵-diphosphetane-2,4-dithione); *d:* $BrCH_2$–CO–COOEt; *e:* NH_3; *f:* $(CF_3CO)_2O$, pyridine; *g:* HN_3, diethyl azodicarboxylate, Ph_3P; *h:* Pd/H_2; *i:* Boc-*R*-Val-S-C_5H_4N; *k:* CF_3COOH; *l:* Boc-*R*-Pro-*R*-Leu-OH, $(PhO)_2PON_3$; *m:* $NaOH/H_2O$; *n:* ethyl 2-aminomethyl-4-thiazolecarboxylate, $(PhO)_2PON_3$; *o:* $NaOH/H_2O$, *p:* $CF_3COOC_6F_5$, pyridine; *q:* CF_3COOH, 4-pyrrolidinopyridine; *r:* H_2O_2, NaOH, pH ≈ 10.

tris(trifluoroacetate) of **14** into a solution of pyrrolidinopyridine (molar ratio 1:3) in alcoholic dioxane at 95°C (70% yield). Hydrolysis of the nitrile **15** to the amide furnished a product **16**[5], which is *not identical* to Dolastatin 3. The spectra[6] of the seven other diastereomers are also not consistent with the data published for Dolastatin 3.

In an analogous way, we have also synthesized the eight diastereomers having reverse order of the amino acids in

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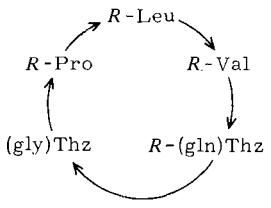
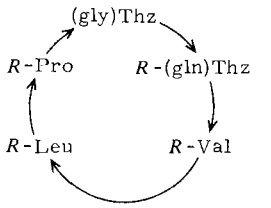


16



R,R,R,R-17

the ring (**17**)[7]. These compounds were also not identical with Dolastatin 3. The following characteristic differences in the NMR spectra of the 16 diastereomers and that of Dolastatin 3 were found: 1) Different chemical shift and coupling for the amide protons, 2) different chemical shift and coupling for the two methylene protons in the 2-position of a thiazole moiety, 3) consistently greater difference in the chemical shift of the two 5-thiazole protons, and 4) different chemical shift for all the methyl protons.

The structure proposed for Dolastatin 3 is therefore not correct. The scheme described for the synthesis of 16 isomers with the structures **16** and **17** in good yields may be used for the economic synthesis of other isomers with different amino acid sequences.

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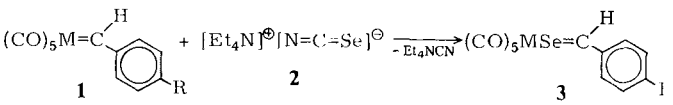
[5] **16**: $[\alpha]_D^{26}$ −44.8 (c=0.11, methanol); TLC R_F=0.16 (CH_2Cl_2/CH_3OH 9:1); MS (high resolution): M_r (found 660.2519 ($C_{29}H_{40}N_8O_6S_2$), M_r (calc.) 660.2512); ^{1}H-NMR (250 MHz, $CDCl_3$/TMS): δ=9.22 (t, J=6 Hz, 1H), 8.45 (d, J=10 Hz, 1H), 8.20 (s, 1H), 8.02 (s, 1H), 7.56 (d, J=8 Hz, 1H), 7.21 (m, 1H), 6.12 (br. s, 1H), 6.0 (br. s, 1H), 5.62 (d, J=6 Hz, 1H), 5.19 (m, 2H), 4.63 (m, 2H), 4.23 (t, J=6 Hz, 1H), 3.89 (m, 1H), 3.57 (m, 1H), 2.44-1.82 (m, 12H), 0.93 (t, J=7 Hz, 6H), 0.65 (d, J=6 Hz, 3H), 0.46 (d, J=6 Hz, 3H).
[6] Spectra were recorded in 5×10^{-3} M solution. Variations in concentration produced no significant change.
[7] *R,R,R,R*-**17**: ^{1}H-NMR (300 MHz, $CDCl_3$/TMS): δ=9.35 (t, J=6 Hz, 1H), 8.72 (d, J=9.3 Hz, 1H), 8.13 (s, 1H), 8.09 (s, 1H), 7.95 (d, J=9.1 Hz, 1H), 6.72 (d, J=5.8 Hz, 1H), 6.32 (br. s, 1H), 5.50 (m, 1H), 5.43 (br. s, 1H), 4.97 (dd, J=6.6 and 14.3 Hz, 1H), 4.53 (dd, J=5.5 and 14.2 Hz, 1H), 4.4 (m, 2H), 4.2 (m, 1H), 3.63 (m, 1H), 3.47 (m, 1H), 2.9−1.3 (m, 12H), 1.06 (m, 6H), 0.9 (d, J=6.5 Hz, 3H), 0.8 (d, J=6.4 Hz, 3H).

Unusual Equilibrium between η^1- and η^2-Isomers of Selenobenzaldehyde Complexes**

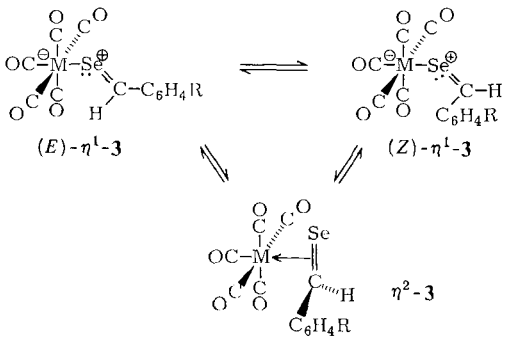
By *Helmut Fischer**, *Siegfried Zeuner*, and *Jürgen Riede*

Seleno- and telluroketones are not stable in the monomeric form; since complexation stabilizes these reactive species, they can be synthesized by reaction of pentacarbonyl(diarylcarbene)chromium and -tungsten with seleno- and tellurocyanate in the ligand spheres of chromium and tungsten, respectively[1,2]. Having recently been able to isolate and characterize benzylidene(pentacarbonyl)chromium and -tungsten complexes[3], it should also be possible to prepare complexes with selenobenzaldehyde, which is likewise unstable in the free form. $(CO)_5W{=}C(H)Ph$ **1a**, which is generated in situ by reaction of $[Et_4N][(CO)_5W{-}C(H)(OMe)Ph]$ with $HBF_4\cdot Et_2O$ at −90°C in dichloromethane, reacts instantaneously with $[Et_4N]NCSe$ **2** in a CH_2Cl_2/pentane mixture at −78°C with formation of $(CO)_5W[Se{=}C(H)Ph]$ **3a**[4].



a, M = W, R = H; **b**, M = W, R = OMe; **c**, M = W, R = CF_3; **d**, M = Cr, R = OMe

Crystals of **3a** are stable for a short while at room temperature. In solution, **3a** is present in an equilibrium of three isomers in which the Se=C(H)Ph-ligand is η^1- or η^2-bonded. Additionally, the η^1-isomer, can either be (*Z*)- or (*E*)-configurated.



The IR spectrum shows nine absorptions of the η^1- and η^2-isomers in the ν(CO) region (hexane): η^1-**3a**: 2068 (w), 1957 (m), 1950 (s), 1944 (m) cm^{-1}; η^2-**3a**: 2096 (s), 2027 (m), 2000 (s), 1985 (vs), 1975 (s) cm^{-1}. The intensity distribution and band positions of the η^1-**3a** absorptions correspond very closely to those of $(CO)_5W(Se{=}CPh_2)$, in which the $Se{=}CPh_2$-ligand is exclusively η^1-bonded. Since Se=C(H)Ph is a poorer σ-donor/π-acceptor than $Se{=}CPh_2$, η^1-**3a** absorbs at somewhat shorter wavelengths. The IR bands of η^2-**3a** lie in a region in which η^2-alkene and -alkyne complexes, e.g. $(CO)_5W(H_2C{=}CH_2)$ and $(CO)_5W(HC{\equiv}CH)$[5], also absorb. On cooling the solution of **3a**, the intensities of the bands of the η^1-isomers decrease, and those of the η^2-isomer increase. That is, the equilibrium (in hexane at room temperature: $K=[\eta^1\text{-}\mathbf{3a}]/[\eta^2\text{-}\mathbf{3a}]=0.2$) shifts in favor of the η^2-form with decreasing temperature. The temperature dependence of the equilibrium constant $K([\eta^1\text{-}\mathbf{3a}]/[\eta^2\text{-}\mathbf{3a}])$ in CH_2Cl_2 yields an enthalpy difference ΔH of 6.6±0.9 kJ/mol. A lower polarity of the solvent also favors the η^2-form.

The ^{1}H-NMR spectrum of **3a** (solvent and standard: CD_2Cl_2) at room temperature shows a multiplet at δ=7.4 for the phenyl protons, as well as a singlet at δ=8.65 for the aldehyde proton (rapid interconversion of the isomers). On cooling, this signal broadens and, eventually, disap-

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pears at ca. −65 °C; then, below −80 °C, a singlet appears at $\delta = 8.2$, which we assign to the η^2-form. A singlet for the aldehyde proton of the η^1-form could not be observed, either because of too low a concentration of the η^1-form—<8% at −80 °C (extrapolated)—or because the signal is excessively broadened due to the *E/Z* isomerization. The ^{13}C-NMR spectrum of **3a** is also temperature-dependent: At −80 °C (CD_2Cl_2), the resonance of the C(Se)-atom appears at $\delta = 74.0$ (for comparison, C(Se) in $(CO)_5W(\eta^1$-$Se{=}CPh_2)$: 240.0[1], $[\{(\eta^5\text{-}C_5H_5)Mn(CO)_2\}_2(\mu_2\eta^2\text{-}Se{=}CH_2)]$: 56.7[6]); at −15 °C on the other hand, a C(Se)-signal can no longer be observed.

η^1-**3a** and η^2-**3a** also differ in the UV/VIS spectrum: η^1-**3a** is deep blue ($\lambda_{max} = 597$ nm), like the η^1-selenoketone complexes, whereas η^2-**3a** is yellow-green ($\lambda_{max} = 425$ nm). Hence, on cooling from room temperature to −78 °C, a solution of **3a** in hexane changes its color reversibly from blue to yellow-green.

The X-ray structure analysis of a crystal of **3a** obtained from hexane at −78 °C shows the η^2-coordination of the Se=C(H)Ph ligand (Fig. 1). The C–Se distance is only slightly shorter than the sum of the carbon and selenium single-bond radii. The selenobenzaldehyde ligand is almost coincident with O4-C4-W-C5-O5, CO(4) and CO(5) are bent away from it, while CO(2) and CO(3) are bent towards it.

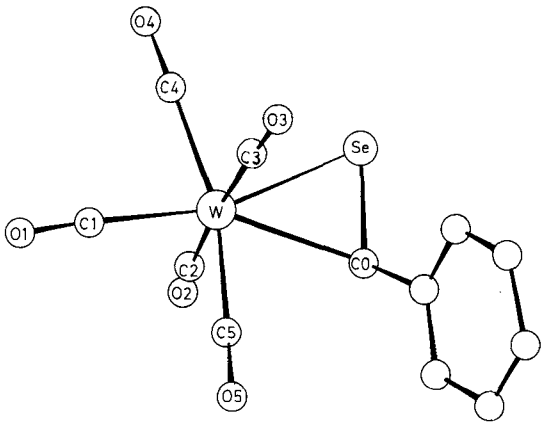

Fig. 1. Structure of the η^2-isomer in the crystal of the selenobenzaldehyde complex **3a**. The asymmetric moiety contains two independent molecules (M1, M2) which, however, on taking the standard deviations into consideration, do not differ significantly. Selected bond lengths [pm] and angles [°], M1 [M2]: W-Se 263.5(2) [263.7(2)], W-C0 240.9(14) [238.4(15)], C0-Se 186.4(13) [187.6(15)], Se-W-C0 43.10(32) [43.51(35)], W-Se-C0 61.98(41) [(61.05(45)]; dihedral angle between the W-Se-C0 and C1-C4-C5 planes: 5° [5°] [7].

The *para*-substituted selenobenzaldehyde complexes of tungsten, **3b** and **3c**, as well as that of chromium, **3d**, can also be prepared in a similar way to that of **3a**[8]. Other than with **3a**, in the case of **3b** the η^1/η^2-equilibrium already lies largely on the side of the η^1-isomer at room temperature, even in apolar solvents, while in the case of **3d**, the η^2-isomer cannot even be detected IR spectroscopically. In **3c**, the η^1-isomer is present only to the extent of <2% in the equilibrium at room temperature in hexane. Thus, increasing donor strength of the aryl groups ($C_6H_4CF_3 < C_6H_5 < C_6H_4OMe$) and replacement of the aldehyde H-atom by an aryl group[1] favor the η^1-isomer over η^2-isomer.

$[(NH_3)_5Ru^{15}NN]^{2\oplus}$ shows an η^1-η^2-η^1-isomerization sequence[9]; in the case of $(\eta^5\text{-}C_5H_5)_2Ti(N_2)$ the η^1- and η^2-isomers could be detected alongside each other below −62 °C by NMR spectroscopy[10]. Generally, $L_nM(XY)$ complexes ($XY = N_2$, O_2, $S{=}CR_2$, $Se{=}CR_2$, $RP{=}CR_2$ etc.) are present *either* in the η^1- *or* the η^2-form. η^1/η^2-Equilibria, which are of importance in a series of stoichiometric and catalytic reactions[11], can now be measured directly as a function of the central metal, the substituents, the solvent, and the temperature.

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[4] Procedure: All operations were carried out under N_2 and in anhydrous solvents. A solution of $[Et_4N][(CO)_5W{-}C(H)(OMe)Ph]$ (1.0 g, 1.7 mmol) in CH_2Cl_2 (30 mL) was treated at −90 °C with a solution of HBF_4 (54% in Et_2O) in CH_2Cl_2 (10 mL). After one minute's stirring the deep red solution was treated, firstly with 100 mL pentane (cooled to −90 °C), and then with 0.4 g (1.7 mmol) $[Et_4N]NCSe$ in 7 mL CH_2Cl_2. The resulting deep blue solution was chromatographed at −75 °C with pentane/CH_2Cl_2 (3:1) on silica gel and the green zone eluted. The green residue remaining after removal of the solvent was recrystallized from pentane at −30 °C. Yield 500 mg (60%).
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[7] **3a**: monoclinic, space group C2/c, $a = 3336.8(10)$, $b = 686.6(2)$, $c = 2376.6(6)$ pm, $\beta = 97.95(2)°$, $Z = 16$, $\rho_c = 2.43$ g cm^{-3}, 3230 reflections, $R_w = 0.046$ (Syntex $P2_1$, $Mo_{K\alpha}$). Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD 50954, the names of the authors, and the journal citation.
[8] **3b**: ^{1}H-NMR ($CDCl_3$, room temperature): $\delta = 12.10$ (s, 1), 7.85 (d, 2), 6.83 (d, 2), 3.83 (s, 3). IR (ν(CO), hexane): η^1-**3b**: 2067 (m), 1954 (s), 1945 (s), 1937 (s) cm^{-1}; η^2-**3b**: 2092 (w), 2024 (vw), 1996 (m), 1982 (m), 1871 (m) cm^{-1}.—**3c**: ^{1}H-NMR (CD_2Cl_2, room temperature): $\delta = 7.53$ (s, 1), 7.48 (m, 4); IR (ν(CO), hexane): η^2-**3c**: 2099 (m), 2032 (w), 2005 (s), 1989 (vs), 1981 (s) cm^{-1}.—**3d**: ^{1}H-NMR ($CDCl_3$, room temperature): $\delta = 13.63$ (s, 1), 8.04 (d, 2), 6.97 (d, 2), 3.93 (s, 3); IR (ν(CO), hexane): η^1-**3d**: 2058 (m), 1956 (s), 1945 (vs) cm^{-1}.
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A Novel Entry to 17α-Bromo- and 17α-Iodoethynyl Steroids

By *Helmut Hofmeister**, *Klaus Annen*, *Henry Laurent*, and *Rudolf Wiechert*

The 17α-ethynyl group in steroids is decisive for their hormonal action upon oral administration[1]. Steroids containing a substituted ethynyl group, e.g. 17α-chloroethynyl derivatives, are also biologically active[2]. 17α-Bromo- and 17α-iodoethynyl compounds of the estradiol series—after exchange with radioactive iodine or bromine—have recently attracted interest for radiological diagnoses in the case of hormone-dependent tumors[3].

Whereas 17α-chloroethynyl steroids[2,4] can be prepared by reaction of 17-keto compounds with lithium chloroacetylide, unfortunately the same synthetic strategy fails in the case of the analogous bromo- and iodo-derivatives **2** and

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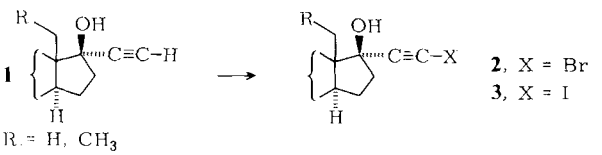
3, respectively. Suitable educts for the synthesis of these analogues, however, are the 17-ethynyl alcohols **1**, whose ethynyl H-atoms can be replaced by a bromine or iodine atom via alkali metal acetylide[2,4,5]. The ethynyl H-atom in steroids can only be substituted by iodine directly, by means of the iodine-morpholine complex[3,4,6]. The hypohalide method[7] frequently employed in acetylene chemistry is unsuitable for the hydrogen/halogen exchange in the case of ethynyl steroids because of the strongly alkaline conditions and, in some cases, the poor solubility of the steroids. The disadvantage of the procedures used so far is that hydroxy and carbonyl groups in the molecule have to be protected. We have now found a simple method for the conversion of the 17α-ethynyl alcohols **1** into the 17α-haloethynyl alcohols **2** and **3** (Table 1), which does not require any protecting groups whatsoever.



When a solution or suspension of the 17-ethynyl compound **1** is allowed to react with equimolar amounts of *N*-bromo- or *N*-iodosuccinimide in the presence of catalytic amounts of silver nitrate, complete conversion into the 17α-haloethynyl compounds **2** and **3**, respectively, usually takes place within 60 min. 1,3-Dibromo-5,5-dimethylhydantoin may be used instead of *N*-bromosuccinimide; *N*-bromoacetamide reacts to some extent with **1**, while bromine and iodine[8] do not react at all. The halogenation reactions are generally carried out in acetone, but, with exception of dimethyl sulfoxide, other solvents such as tetrahydrofuran, ethanol, or 1-methyl-2-pyrrolidone can be used. Suitable catalysts are any of the silver salts which dissociate in the solvent (silver salt : steroid ratio ≈ 1 : 10).

Remarkably, *N*-chlorosuccinimide and other *N*-chloro compounds do not react under the above mentioned conditions. The method can also be used in the case of other alkynes (see the last two examples[9–11] listed in Table 1). We assume that the silver ions activate the terminal hydrogen atom for a hydrogen exchange by formation of a π-complex with the triple bond[12]; in the absence of catalyst, *N*-bromosuccinimide does not react with alkynes.

Experimental

A solution (or suspension) of the alkyne (3.0 mmol) in acetone (20 mL) is treated at room temperature with 3.5 mmol *N*-bromo- or *N*-iodosuccinimide and 50 mg silver nitrate. After 15—60 min (Table 1), the reaction mixture is poured with stirring into ice-water and the precipitate that is formed is filtered off and dissolved in ethyl acetate. The resulting solution is washed with water, dried, evaporated to dryness in vacuo, and the final product is purified by crystallization.

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CAS Registry numbers:
1a (R = H), 434-03-7; **1b** (R = H), 68-22-4; **1c** (R = H), 68-23-5; **1d** (R = CH_3), 797-63-7; **1e** (R = CH_3), 60282-87-3; **1f** (R = CH_3), 54048-10-1; **1g** (R = CH_3), 54024-22-5; **1h** (R = H), 72-33-3; **1i** (R = H), 57-63-6; **1j** (benzoate) (R = H), 434-03-7; **2a**, 4288-39-5; **2b**, 4288-68-0; **2c**, 4288-43-1; **2d**, 91781-30-5; **2e**, 91781-31-6; **2f**, 91781-32-7; **2g**, 91781-33-8; **2h**, 4652-89-5; **2i**, 4610-08-6; **3a**, 15505-87-0; **3b**, 91781-34-9; **3c**, 91781-35-0; **3d**, 91781-36-1; **3e**, 91798-46-8; **3f**, 91781-37-2; **3h**, 91798-47-9; **3i**, 73309-85-0; **4**, 932-87-6; **5**, 14420-47-4; PhC≡CH, 536-74-3; $AgNO_3$, 7761-88-8; 2-(2-propynyloxy)tetrahydro-2*H*-pyran.

Table 1. 17α-Bromo- and 17α-iodoethynyl steroids **2** and **3** prepared from the 17α-ethynyl alcohols **1**.

Product [a]	*t* [min] [b]	Yield [%] [c]	M.p. [°C] [d] (B.p. [°C/torr])	$[\alpha]_D^{22}$ [e]	Educt
17α-Bromoethynyl-17β-hydroxy-4-androsten-3-one **2a**	40	88	183.7	+ 6.6	[13]
17β-Hydroxy-17α-iodoethynyl-4-androsten-3-one **3a**	45	79	163.8	− 2.4	[13]
17α-Bromoethynyl-17β-hydroxy-4-estren-3-one **2b**	15	83	184.6	− 47.2	[14]
17β-Hydroxy-17α-iodoethynyl-4-estren-3-one **3b**	30	79	168.0	− 69 (pyridine)	[14]
17α-Bromoethynyl-17β-hydroxy-5(10)-estren-3-one **2c**	45	81	166.0	+ 105	[15]
17β-Hydroxy-17α-iodoethynyl-5(10)-estren-3-one **3c**	30	75	124.0	+ 90.2	[15]
17α-Bromoethynyl-17β-hydroxy-18-methyl-4-estren-3-one **2d**	20	88	206.4	− 51	[16]
17β-Hydroxy-17α-iodoethynyl-18-methyl-4-estren-3-one **3d**	30	86	157.0	− 59.2	[16]
17α-Bromoethynyl-17β-hydroxy-18-methyl-4,15-estradien-3-one **2e**	15	82	106.5	−219.6	[17]
17β-Hydroxy-17α-iodoethynyl-18-methyl-4,15-estradien-3-one **3e**	15	77	165.0	−268.8 (pyridine)	[17]
17α-Bromoethynyl-17β-hydroxy-18-methyl-11-methylene-4-estren-3-one **2f**	30	86	203.8	+ 19.2	[18]
17β-Hydroxy-17α-iodoethynyl-18-methyl-11-methylene-4-estren-3-one **3f**	30	75	179.0	+ 1.1	[18]
17α-Bromoethynyl-18-methyl-11-methylene-4-estren-17β-ol **2g** [f]	45	51	168.8	+ 6.4	[18]
17α-Bromoethynyl-3-methoxy-1,3,5(10)-estratrien-17β-ol **2h**	30	84	172.6	− 17.5	[13]
17α-Iodoethynyl-3-methoxy-1,3,5(10)-estratrien-17β-ol **3h**	60	86 [h]	145.8	− 24.3	[13]
17α-Bromoethynyl-1,3,5(10)-estratriene-3,17β-diol **2i** [f]	60	56	169.6	− 20	[13]
3-Benzoyloxy-17α-iodoethynyl-1,3,5(10)-estratrien-17β-ol **3i**	30	65	184.0	− 16	[3]
1-Bromo-2-phenylacetylene **4** [9, 10] [g]	40	61	(56—57/6)	—	—
2-(3-Bromo-2-propynyloxy)tetrahydro-2*H*-pyran **5** [11] [g]	40	59	(92/6)	—	[19]

[a] All compounds were characterized by elemental analysis and by UV, IR, and NMR data. [b] Reaction medium: acetone. [c] After recrystallization from acetone/hexane. [d] Mettler FP11; 2°/min; substances melt with decomposition. [e] $c = 0.5$; unless otherwise stated, in chloroform. [f] Purified chromatographically on silica gel (0.04—0.063 mm, Merck) with hexane/ethyl acetate by the gradient method. [g] Yields not optimized. [h] Recrystallized from diisopropyl ether.

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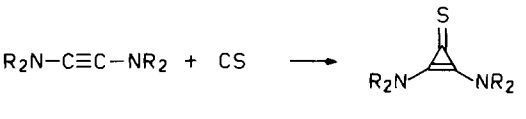
[17] H. Hofmeister, R. Wiechert, K. Annen, H. Laurent, H. Steinbeck, DBP 2546062 (October 10, 1975) Schering AG; *Chem. Abstr. 87* (1977) 168265k.
[18] A. J. Van den Broek, C. Van Bokhoven, P. M. J. Hobbelen, J. Leemhuis, *Recl. Trav. Chim. Pays-Bas 94* (1975) 35.
[19] H. B. Henbest, E. R. H. Jones, I. M. S. Walls, *J. Chem. Soc. 1950*, 3646.

[2+1]-Cycloadditions of Ynamines and Ynediamines to Carbon Monosulfide**

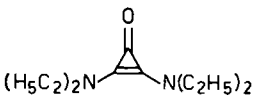
By *Adolf Krebs**, *Andreas Güntner*, *Alexander Senning**, *Ejner K. Moltzen*, *Kenneth J. Klabunde*, and *Michael P. Kramer*

Until recently carbon monosulfide (CS) was little used as a reagent in organic synthesis, its principal application being insertion reactions into S–Cl bonds[1,2]. We wish to report the first [2+1]-cycloaddition of alkynes to CS, yielding the cyclopropenethiones **2a**, **b** and **5**. Since the resonance stabilization of bis(dialkylamino)cyclopropenethiones[3] should make itself felt even in the transition state of the addition reaction, we used the extremely electron-rich ynediamines **1a**, **b** and the ynamine 1-diethylamino-1-propyne **4** as scavengers.

Carbon monosulfide, generated by decomposition of CS_2 in a discharge tube (8000 V) at 10^{-2}–10^{-1} torr[1], was passed over the surface of an approximately 1 M solution



1a: R = CH_3 **2a**: R = CH_3
b: R = C_2H_5 **b**: R = C_2H_5



3

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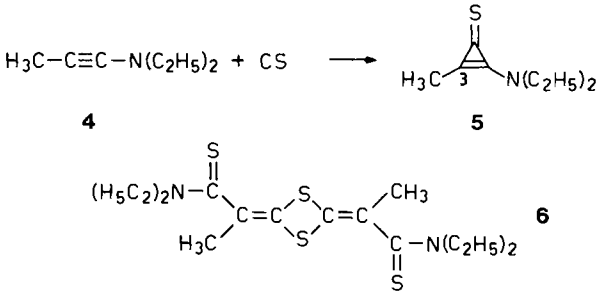
[**] Chemistry of Carbon Monosulfide in Solution, Part 3.—Part 2: [2].

of **1a**, **b** or **4** in toluene at −78 °C. Use of a cold trap (−95 °C; at lower temperatures solid CS freezes out) does not separate out undecomposed CS_2 completely; thus the yields of CS adducts were diminished by reaction of **1a**, **b** or **4** with CS_2.

Compound **2a** was obtained in 67% yield (relative to **1a**; m.p. = 147 °C) and identified by comparison with an authentic sample[4]; **2b** (32%; m.p. = 49 °C) was identical with a sample prepared by treatment of the corresponding cyclopropenone **3**[5] with P_4S_{10}[6].

From the reaction of CS with **4** we obtained the novel cyclopropenethione **5** (24%; m.p. = 51–53 °C), which was characterized by spectroscopy and elemental analysis[7]; in addition **4** and CS_2 formed the known desaurin **6**[8].



4 **5**

6

With diphenylacetylene only polymerization of CS occurred[1].

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CAS Registry numbers:
1a, 5907-90-4; **1b**, 5323-13-7; **2a**, 52910-77-7; **2b**, 91295-97-5; **4**, 4231-35-0; **5**, 91295-98-6; **6**, 91295-99-7; CS, 2944-05-0.

[1] K. J. Klabunde, M. P. Kramer, A. Senning, E. K. Moltzen, *J. Am. Chem. Soc. 106* (1984) 263.
[2] E. K. Moltzen, A. Senning, M. P. Kramer, K. J. Klabunde, *J. Org. Chem.*, in press.
[3] Cf. Z. Yoshida, *Top. Curr. Chem. 40* (1973) 47.
[4] Z. Yoshida, H. Konichi, H. Ogoshi, *Isr. J. Chem. 21* (1981) 139.
[5] C. Wilcox, R. Breslow, *Tetrahedron Lett. 21* (1980) 3241.
[6] By analogy to the preparation of 2,3-diphenylcyclopropenethione described by Y. Kitahara, M. Funamizu, *Bull. Chem. Soc. Jpn. 37* (1964) 1897.—**2b**: MS: *m/z* 212 ($M^{\oplus}$; 100%); ^{1}H-NMR (60 MHz, CD_3CN): δ = 1.25 (t, 12H, CH_3), 3.28 (q, 8H, CH_2); ^{13}C-NMR (100.62 MHz, CD_3CN): δ = 14.68 (CH_3), 46.67 (CH_2), 133.32 (olef. C), 133.58 (C=S); IR (KBr): 1890 cm^{-1}.
[7] **5**: MS: *m/z* 155 ($M^{\oplus}$, 63%), ^{1}H-NMR (60 MHz, $CDCl_3$): δ = 1.20 (t, 3H, CH_3), 1.30 (t, 3H, CH_3), 2.16 (s, 3H, CH_3–C3), 3.28 (q, 2H, CH_2), 3.47 (q, 2H, CH_2); ^{13}C-NMR (25.2 MHz, $CDCl_3$): δ = 9.43 (CH_3–C3), 13.79, 14.58 (CH_3), 46.53, 46.71 (CH_2), 128.56, 151.76 (olef. C), 161.27 (C=S); IR (KBr): 1840 cm^{-1}.
[8] A. Senning, R. G. Hazell, *Sulfur Lett. 2* (1984) 173.

Surprising Stability of Nucleophilic Cr^{III}-Alkylating and Cr^{III}-Allylating Reagents towards Ethanol and Water**

By *Thomas Kauffmann**, *Renate Abeln*, and *Dorothea Wingbermühle*

We recently found that the methylenemolybdenum reagents $ClMo(O)=CH_2$ and $Cl_3Mo=CH_2$ are able to olefin-

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[**] Transition-Metal Activated Organic Compounds, Part 17. This work was supported by the Deutsche Forschungsgemeinschaft and by the Fonds der Chemischen Industrie.—Part 16: [1b].

ate carbonyls even in media containing ethanol or water (70 to 220 mol protic solvent per mol Mo=C compound)[1]; the question now arises whether alkyl-transition metal compounds also exist which are able to alkylate carbonyls in alcoholic or aqueous media[2]. Nucleophilic alkylating reagents which are inert towards OH groups would be of particular interest for the alkylation of hydroxyaldehydes and hydroxyketones.

The chromium(III) compounds **1**[3], which are stable in aqueous solution at room temperature, do not alkylate aldehydes. The alkylchromium(III) reagents **2** and **3** which alkylate aldehydes in tetrahydrofuran (THF)[4] do this also in the presence of ethanol or water. As indicated by a series of experiments with heptanal (Fig. 1), addition of ethanol or water increases even the alkylating effect of the methyl compound **2**. The best yields were obtained in the reactions of the bisallyl compound **4**[5] with heptanal and benzaldehyde in the presence of ethanol. The bis-2-butenyl compound **5** reacts with ethanol (molar ratio 1 : 1) to yield an active species which is stable towards protonolysis.

$[(H_2O)_5Cr-R]^{2\oplus}$ $(THF)_3Cl_2Cr-R$ $(THF)_3ClCrR_2$

1, R = alkyl **2**, R = CH_3 **4**, R = $CH_2-CH=CH_2$

3, R = $(CH_2)_3CH_3$ **5**, R = $CH_2-CH=CH-CH_3$/ $CH(CH_3)-CH=CH_2$

$$R'-CHO + n\ EtOH\ (or\ H_2O) \xrightarrow[2)\ H_2O\ (large\ excess)]{1)\ 3\ \mathbf{2}\ or\ 1\ \mathbf{4}\ or\ \mathbf{5}} R'-\underset{\displaystyle OH}{\underset{|}{C}}H-R$$

6

Scheme 1.

The reactions (Fig. 1, Scheme 2) indicate that, despite a 2—10 fold excess of protic solvent (relative to Cr-alkyl residue; allyl and 2-butenyl = special alkyl), aldehyde can still be alkylated in high yield.

The finding that addition of 1–3 mol protic solvent maximizes the yield (or for reagent **5** increases the yield, which remains constant upon further addition) indicates that 1–3

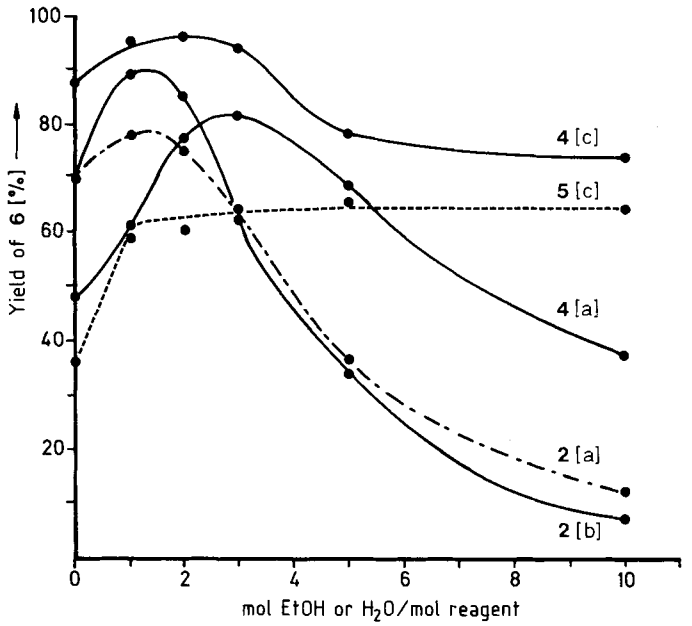

Fig. 1. The reactions shown in Scheme 1 are in THF. [a] Heptanal/EtOH added to the reaction solution at −70°C and warmed to 20°C within ca. 15 h. [b] Heptanal/H_2O added to reaction solution at 0°C, and then as described for [a]. [c] Reaction as described for [a], but with benzaldehyde instead of heptanal.

$C_6H_{13}-CHO + 3\ \mathbf{2} + 6\ EtOH\ (or\ 6\ H_2O) \longrightarrow$

$C_6H_{13}-CH(OH)-CH_3$ 78% (85%)

$Ph-CHO + 1\ \mathbf{4} + 10\ EtOH\ (or\ 20\ H_2O) \longrightarrow$

$Ph-CH(OH)-CH_2CH=CH_2$ 74% (52%)

$Ph-CHO + 1\ \mathbf{5} + 10\ EtOH \longrightarrow$

$Ph-CH(OH)-CH(CH_3)-CH=CH_2$ 62%

7 [5]

Scheme 2.

solvent molecules are incorporated into the ligand sphere of a reagent molecule, without leading to cleavage of the Cr—C bond. In this respect, THF molecules may be displaced or Cr-ligand-Cr bridges ruptured. Driving force for the reaction is probably the formation of a more stable solvent sheath.

Alkylation of heptanal in ethanol-containing media was effected also by the Ti^{IV} reagents **8** and **9**[5] (Scheme 3). However, ethanol led, not to an increase, but rather to a decrease in the yield of alkylation product. Nevertheless, these experiments indicate that the cleavage of a Ti-alkyl bond by alcoholic groups is also surprisingly slow compared to the aldehyde alkylation. Similar results were found with reagents **10**—**12**[5].

$C_6H_{13}-CHO + 3\ Cl_3Ti-CH_3 + 6\ EtOH \longrightarrow$

8

$C_6H_{13}-CH(OH)-CH_3$ 50%

$Ph-CHO + 1\ (iPrO)_3Ti-CH_2CH=CH_2 + 3\ EtOH \longrightarrow$

9

$Ph-CH(OH)-CH_2CH=CH_2$ 55%[6]

$Cl-V(O)(CH_2CH=CH_2)_2$ $(EtO)_3Nb(CH_3)_2$ $Mn(CH_2CH=CH_2)_2$

10 **11** **12**

Scheme 3.

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CAS Registry numbers:
2, 36153-92-1; **4**, 91686-98-5; **5** (R = $CH_2CH=CHCH_3$), 91686-99-6; **5** (R = $CH(CH_3)CH=CH_2$), 91687-01-3; **8**, 2747-38-8; **9**, 22378-84-3; **10**, 91687-00-2; **11**, 82941-69-3; **12**, 78969-07-0; C_6H_{13}-CHO, 111-71-7; Ph-CHO, 100-52-7.

[1] a) T. Kauffmann, P. Fiegenbaum, R. Wieschollek, *Angew. Chem. 96* (1984) 500; *Angew. Chem. Int. Ed. Engl. 23* (1984) 531; b) T. Kauffmann, G. Kieper, *ibid. 96* (1984) 502; *23* (1984) 532.

[2] In this connection, water-stable alkyl-transition metal complexes should be mentioned: I. Feinstein-Jaffe, S. F. Pedersen, R. R. Schrock, *J. Am. Chem. Soc. 105* (1983) 7176, and literature cited therein.

[3] A. Segnitz in Houben-Weyl-Müller: *Methoden der organischen Chemie, 4th edit., vol. 13/7*, Thieme, Stuttgart 1975, p. 384.

[4] T. Kauffmann, A. Hamsen, C. Beirich, *Angew. Chem. 94* (1982) 145; *Angew. Chem. Int. Ed. Engl. 21* (1982) 144.

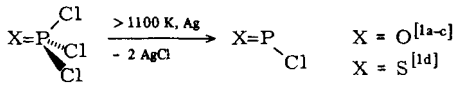
[5] All the alkyl-transition metal reagents were prepared in situ: **2** from $CrCl_3$ and methyllithium; **4** and **5** from $CrCl_3$ and allyl- and 2-butenylmagnesium bromide, respectively; **8**—**12** from $TiCl_4$, $(iPrO)_3TiCl$, $V(O)Cl_3$, $(EtO)_3NbCl_2$, and $MnCl_2$, respectively. In addition to aldehydes, **4** also reacts smoothly with ketones. Product **7** obtained from **5** and benzaldehyde is a *threo-erythro*-mixture (1 : 1.2): T. Kauffmann, C. Beirich, unpublished.—For the diastereoselectivity of a 2-butenylchromium compound of unknown structure (from $CrCl_2$ and 2-butenyl bromide), see C. T. Buse, C. H. Heathcock, *Tetrahedron Lett. 1978*, 1685.

[6] T. Kauffmann, C. Pahde, unpublished.

O=P–Cl and S=P–Cl: Gas-Phase Ionization**

By *Michael Binnewies**, *Bahman Solouki*, *Hans Bock**, *Ralf Becherer*, and *Reinhart Ahlrichs**

O=P–Cl and S=P–Cl[1] each contain 18 valence electrons and are therefore iso(valence)electronic with compounds exhibiting bent structures[2] such as ONCl, OSO, OOO, FCF, and NSF. They are also of interest as prototype molecules of recently prepared compounds such as the diphosphenes R–P=P–R[3], in which phosphorus of coordination number 2 is kinetically stabilized by bulky substituents. O=P–Cl and S=P–Cl can be prepared in the gas phase by dechlorination of the corresponding trichlorides with silver turnings above 1100 K.



Both compounds have already been detected in the gas phase by mass spectroscopy and their structures elucidated by IR spectroscopy after isolation[1c,e] in an argon matrix at 15 K[1c,e,4]. We report here the PE spectroscopic ionization patterns[5] and their assignments based on ab initio SCF calculations[6].

Upon pyrolysis at 1150 K, the ionization pattern of the starting material $SPCl_3$[7] disappears completely (Fig. 1a, b; cf., e.g., the bands at 10.6, 12.9, and 15.2 eV). The pyrolyzate contains PCl_3, identified by PE spectroscopy as side product[1a,7]; its ionization bands can be eliminated by computer subtraction (Fig. 1b, c).

The He(I)PE spectra of SPCl and OPCl between 9 and 19 eV thus obtained each display six ionization bands, in accord with the reliable (np_E+1s_H) valence-electron counting rule[7] and with the assignment used for the ab initio SCF calculations[6]. Comparison of the corresponding radical cation states (Fig. 1c, d, dotted connecting lines) shows that the smaller effective nuclear charge of the sulfur atom causes a lowering of all ionization energies by approximately 1 eV. From the MO contour-line diagrams (Fig. 1e), the $M^{\odot\oplus}$ ground states $\tilde{X}(^2A')$ of both molecules can be characterized as electron pair ionizations with a major P-contribution. In both cases, a π state $\tilde{A}(^2A'')$ follows, with predominant Cl-contribution in OPCl and S-contribution in SPCl; for the π states at 13.3 and 14.3 eV, respectively, these relations are inverted. The third $M^{\odot\oplus}$ states $\tilde{B}(^2A')$ correspond within the MO picture to the antibonding combinations of the electron pairs $n_{Cl}-n_O$ and n_S-n_{Cl}. In general, the radical cation states of A' symmetry are characterized at low ionization energies by a larger contribution of the electron lone-pairs and at higher energies by σ-bonding electrons[2,6].

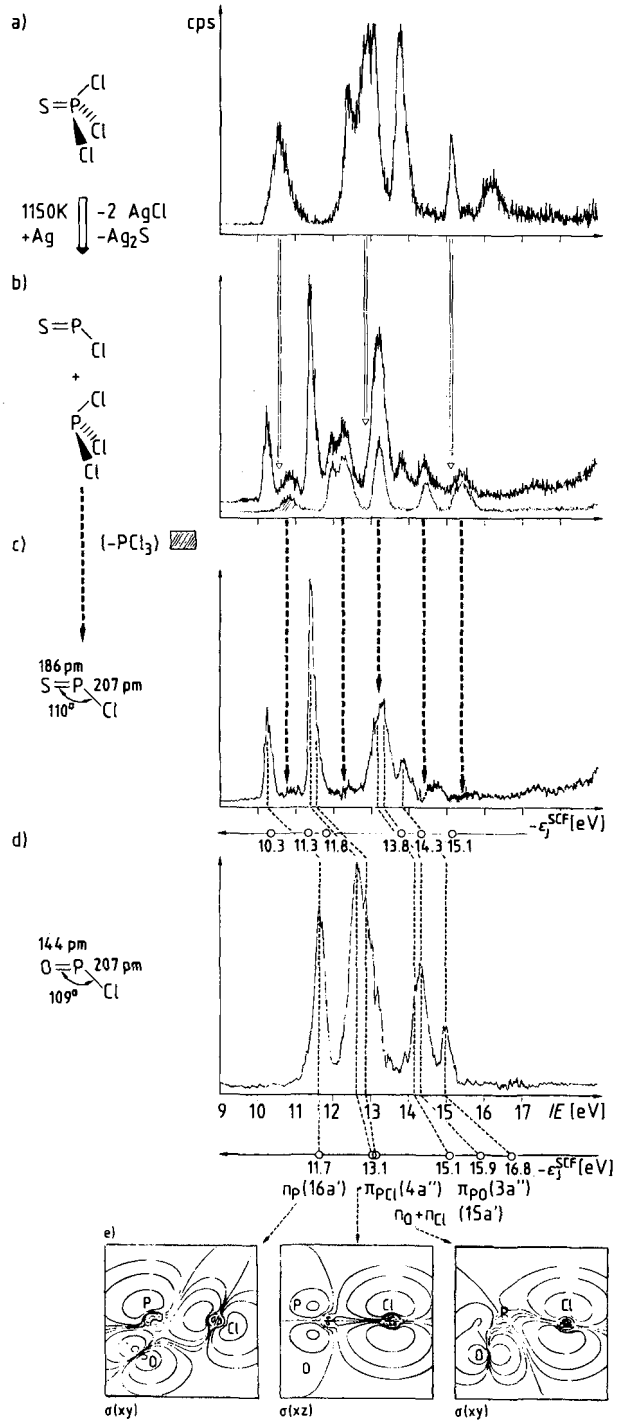


Fig. 1. He(I)PE spectra between 9 and 19 eV of a) $SPCl_3$ at 300 K and b) the product mixture, after reaction with silver at 1150 K, consisting mainly of SPCl and PCl_3 [5]. The PE spectrum c) of SPCl was obtained by computer-subtraction (----→) of the ionization bands of the side product PCl_3 (hatched) [7]. Use of *Koopmans'* correlation $IE_n^v = -\varepsilon_j^{SCF}$ permits assignment of the bands to the ab initio SCF eigenvalues [6]. d) The ionization pattern of OPCl is obtained in an analogous way (subtraction of the PE spectrum of HCl, presumably formed by surface reactions). The assignment is corroborated by comparison with the corresponding states of the radical cation of SPCl as well as by *Koopmans'* correlation with the ab initio SCF eigenvalues [6]. e) The three $M^{\odot\oplus}$ states of lowest energy are characterized by MO contour-line diagrams. The structural data listed for SPCl and OPCl are those calculated for the minimum total energy [6] in each case.

The structural data of SPCl and OPCl calculated for the respective minima of the total energies (Fig. 1) differ only slightly from those of the educts $SPCl_3$ and $OPCl_3$[8]: the influence of the electron pair at the P atom generated by

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[**] Gas-Phase Reactions, Part 47. This work was supported by the Länder Hessen, Nordrhein-Westfalen, and Baden-Württemberg, the Deutsche Forschungsgemeinschaft, and the Fonds der Chemischen Industrie.— Part 46: H. Bock, P. Rosmus, B. Solouki, G. Maier, *J. Organomet. Chem.*, in press.

chlorine split-off is manifested by contraction of the OPCl angle from 115 to 109° and by that of the SPCl angle from 116 to 110°C. According to the calculations, the P=O and P=S bond lengths are 1—2 pm shorter and the PCl distances 6 pm longer than in the corresponding trichlorides.

The dehalogenation of the oxide chlorides is due to the thermal instability of Ag_2O above 570 K; by this route, numerous other molecules containing central atoms with low coordination number can be prepared, e.g. OPF[1a], $OPBr$[1a], SPF[1a], $OAsCl$[1f], $OSbCl$[1f], and O_2PCl[1g].

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German version: *Angew. Chem. 96* (1984) 704

[1] a) M. Binnewies, Habilitationsschrift, Universität Münster 1984; b) *Thermochim. Acta 67* (1983) 387; c) M. Binnewies, M. Lakenbrink, H. Schnöckel, *Z. Anorg. Allg. Chem. 497* (1983) 7; d) M. Binnewies, *ibid. 507* (1983) 66; e) H. Schnöckel, M. Lakenbrink, *ibid. 507* (1983) 70; f) M. Binnewies, *ibid. 507* (1983) 32; g) cf. also M. Binnewies, *ibid. 505* (1983) 77.

[2] A. D. Walsh, *J. Chem. Soc. 1953*, 2266. Cf. also R. J. Buenker, S. D. Peyerimhoff, *Chem. Rev. 74* (1974) 127, and literature cited therein.

[3] Review: A. H. Cowley, *Polyhedron 3* (1984) 389; see also M. Yoshifuji, J. Shina, N. Inamoto, *J. Am. Chem. Soc. 103* (1981) 4587; *104* (1982) 6167; B. Cetinkaya, P. B. Hitchcook, M. L. Lappert, A. J. Thorne, H. Goldwhite, *J. Chem. Soc. Chem. Commun. 1982*, 691; G. Bertrand, C. Couret, J. Escudie, M. Majid, J. P. Majoral, *Tetrahedron Lett. 23* (1982) 3567; A. H. Cowley, J. E. Kilduff, T. H. Newman, M. Pakulski, *J. Am. Chem. Soc. 104* (1982) 5820; C. Couret, J. Escudie, J. Satgé, *Tetrahedron Lett. 23* (1982) 4941; E. Niecke, R. Rüger, *Angew. Chem. 95* (1983) 154; *Angew. Chem. Int. Ed. Engl. 22* (1983) 155; E. Niecke, R. Rüger, M. Lysek, S. Pohl, W. Schoeller, *ibid. 95* (1983) 495 and *22* (1983) 486; *Angew. Chem. Suppl. 1983*, 639, and references cited therein.

[4] E. Lindner, K. Auch, W. Hiller, R. Fawzi (*Angew. Chem. 96* (1984) 287; *Angew. Chem. Int. Ed. Engl. 23* (1984) 320) succeeded in trapping a thioxophosphane intermediate in the dehalogenation of dichloro(methyl)thioxophosphorane with Mg in the presence of $Mn_2(CO)_{10}$.

[5] PE spectrometer: Leybold Heraeus UPG 200 (resolution 20 meV, calibration with $^2P_{3/2}(Ar) = 15.76$ eV). The high-temperature inlet system (cf. B. Solouki, H. Bock, R. Appel, A. Westerhaus, G. Becker, G. Uhl, *Chem. Ber. 115* (1982) 3747) contains the silver turnings. PE spectra were recorded and subtracted using a PDP 11/40 computer.

[6] The ab initio SCF calculations were carried out at the Hochschulrechenzentrum Karlsruhe, using basis sets of "double zeta" quality augmented by d-polarization functions. The following basis sets were employed: For O (9s, 5p, 1d) contracted to (5s, 3p, 1d) with $\eta_d = 1.25$, and for 2nd row elements (11s, 7p, 1d) contracted to (7s, 4p, 1d) with $\eta_d = 0.50$ (P), 0.55 (S), and 0.65 (Cl). The structures calculated for the minima of total energy should be precise to ±2° and ±2 pm. Since in *Koopmans'* correlations, reorganization- and electron-correlation effects are not considered, changes in the sequences in the assignment of energetically closely lying radical cation states cannot be precluded.

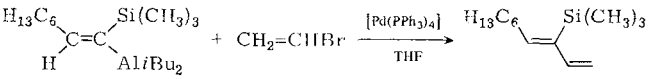
[7] For the assignment of the PE spectra of $SPCl_3$ and PCl_3 cf. K. Wittel, H. Bock in S. Patai, Z. Rappaport: *The Chemistry of Functional Groups, Suppl. D*, Wiley, London 1983, p. 1560 and 1563, and literature cited therein.

[8] Cf. e.g. A. F. Wells: *Structural Inorganic Chemistry, 4th edit.*, Clarendon, Oxford 1975, p. 679.

Metal-Catalyzed Carbonylations of Benzyl and Aryl Bromides in the Presence of Aluminum Alkoxides; A Straightforward Ester Synthesis**

By *Howard Alper**, *Shlomo Antebi*, and *James B. Woell*

There has been increasing interest in the use of organometallic complexes as catalysts for reactions involving main-group organometallic compounds[1]. *Negishi* et al.[2] have described the $[Pd(PPh_3)_4]$-catalyzed cross-coupling reaction of α-hetero-substituted alkenylaluminum (and -zinc) compounds with vinyl or aryl halides[3].



Here, we report the first examples of metal-catalyzed reactions of aluminum alkoxides, relatively inexpensive, easy-to-handle compounds which have been used in several syntheses[4–9].

Benzylic bromides react with aluminum ethoxide and carbon monoxide in heptane in the presence of catalytic quantities of 1,5-hexadienerhodium(I) chloride dimer ([1,5-hd]RhCl]$_2$) to afford ethyl esters. This reaction occurs under mild conditions (75°C, 1 atm), is easy to execute and work-up, and product yields are good (Table 1). It is applicable to other aluminum compounds, including aluminum isopropoxide and aluminum *sec*-butoxide, but only starting material was recovered when aluminum *tert*-butoxide was used as the reactant. The corresponding alcohol cannot be substituted for the aluminum alkoxide in these reactions, and the presence of the Rh-catalyst is essential. Chlorides are much less reactive than bromides since, for example, ethyl phenylacetate is formed in 21% yield from benzyl chloride compared with a 100% yield in the case of benzyl bromide.

β-Bromostyrene undergoes carbonylation with aluminum ethoxide in the presence of the Rh-catalyst, affording

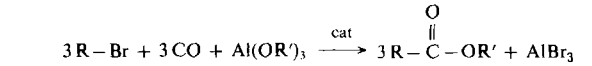


Table 1. Catalytic carbonylation of benzyl and aryl bromides with CO and aluminum alkoxides.

RBr	R′ in Al(OR′)$_3$	Cat. [a]	Product [b]	Yield [%] [c]
$PhCH_2Br$	C_2H_5	Rh	$PhCH_2CO_2C_2H_5$	100
	$CH(CH_3)_2$	Rh	$PhCH_2CO_2CH(CH_3)_2$	52
	$CH(CH_3)C_2H_5$	Rh	$PhCH_2CO_2CH(CH_3)C_2H_5$	68
p-$CH_3C_6H_4CH_2Br$	C_2H_5	Rh	*p*-$CH_3C_6H_4CH_2CO_2C_2H_5$	63
m-$CH_3C_6H_4CH_2Br$	C_2H_5	Rh	*m*-$CH_3C_6H_4CH_2CO_2C_2H_5$	82
o-$CH_3C_6H_4CH_2Br$	C_2H_5	Rh	*o*-$CH_3C_6H_4CH_2CO_2C_2H_5$	75
2-NpCH$_2$Br [d]	C_2H_5	Rh	2-$NpCH_2CO_2C_2H_5$	70
	$CH(CH_3)_2$	Rh	2-$NpCH_2CO_2CH(CH_3)_2$	50
	$CH(CH_3)C_2H_5$	Rh	2-$NpCH_2CO_2CH(CH_3)C_2H_5$	91
PhCH=CHBr	C_2H_5	Rh	$PhCH{=}CHCO_2C_2H_5$	25
	C_2H_5	Rh/Pd	$PhCH{=}CHCO_2C_2H_5$	66
PhBr	C_2H_5	Rh/Pd	$PhCO_2C_2H_5$	80
1-NpBr [d]	C_2H_5	Rh/Pd	1-$NpCO_2C_2H_5$	78
	$CH(CH_3)_2$	Rh/Pd	1-$NpCO_2CH(CH_3)_2$	60

[a] Rh = [(1,5-hd)RhCl]$_2$ (1,5-hd = 1,5-hexadiene); Pd = $[Pd(PPh_3)_4]$. [b] Products were identified by comparison of spectral data with those for authentic materials. [c] Purified products. [d] Np = naphthyl.

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[**] We are grateful to British Petroleum for support of this research.

the ethyl cinnamate in only 25% yield; however, with the bimetallic catalyst $[(1,5\text{-hd})RhCl]_2/[(PPh_3)_4Pd]$ (1.5 : 1.0) and a reaction temperature of 150°C the yield of ester increases to 66%. Similarly, aryl bromides such as 1-bromonaphthalene and bromobenzene can be converted into esters in reasonable yields using the bimetallic catalysis system (Table 1), a reaction which does not proceed when only the rhodium(I) or palladium(0) catalyst is used. Alkyl bromides, e.g., 1-bromoheptane, fail to react in the presence of the monometallic or bimetallic catalysts.

Experimental

Carbon monoxide is bubbled through a solution of the Rh-catalyst (0.22 mmol), aluminum alkoxide (2.5 mmol), and halide (2.0 mmol) in 3 mL heptane. The reaction mixture is stirred for 16 h at 75° and then cooled to 0°C. Ether (10 mL) is added, followed by 1 M NaOH (5 mL), and the mixture filtered through Celite. Extraction with ether affords the crude ester, which is purified by flash chromatography. In the case of the bimetallic catalyst, $[(1,5\text{-hd})RhCl]_2$ (0.22 mmol) and $[(PPh_3)_4Pd]$ (0.15 mmol) are used.

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CO, 630-08-0; $[(1,5\text{-hd})RhCl]_2$, 32965-49-4; $Pd(PPh_3)_4$, 14221-01-3; $PhCH_2Br$, 100-39-0; *p*-$MeC_6H_4CH_2Br$, 104-81-4; *m*-$MeC_6H_4CH_2Br$, 620-13-3; *o*-$MeC_6H_4CH_2Br$, 89-92-9; 2-$NpCH_2Br$, 939-26-4; $PhCH{=}CHBr$, 103-64-0; PhBr, 108-86-1; 1-NpBr, 90-11-9; $Al(OEt)_3$, 555-75-9; $Al(i\text{-}PrO)_3$, 555-31-7; $Al(sec\text{-}BuO)_3$, 2269-22-9; $PhCH_2C(O)OEt$, 101-97-3; $PhCH_2C(O)O\text{-}i\text{-}Pr$, 4861-85-2; $PhCH_2C(O)O\text{-}sec\text{-}Bu$, 5436-58-8; *p*-$MeC_6H_4CH_2C(O)OEt$, 14062-19-2; *m*-$MeC_6H_4CH_2C(O)OEt$, 40061-55-0; *o*-$MeC_6H_4CH_2C(O)OEt$, 40291-39-2; 2-$NpCH_2C(O)OEt$, 2876-70-2; 2-$NpCH_2C(O)O\text{-}i\text{-}Pr$, 91759-48-7; 2-$NpCH_2C(O)O\text{-}sec\text{-}Bu$, 91759-49-8; $PhCH{=}CHC(O)OEt$, 103-36-6; $PhC(O)OEt$, 93-89-0; 1-NpC(O)OEt, 3007-97-4; 1-NpC(O)O-*i*-Pr, 951-19-9; $PhCH_2Cl$, 100-44-7.

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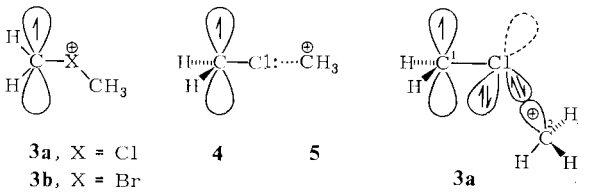
Reactivity of $CH_2{-}X{-}CH_3^{\oplus\odot}$ (X = Cl, Br) with Electrophiles and Nucleophiles in the Gas Phase, a Fourier Transform Ion Cyclotron Resonance Investigation**

By *Thomas Weiske, Hans van der Wel, Nico M. M. Nibbering,* and *Helmut Schwarz**

Radical cations of type **1**, also called ion/dipole complexes in the literature and whose neutral counterparts **2** are unknown in many cases, appear to play a central role as intermediates not only in unimolecular decomposition reactions, but also in the formation of organic molecules in interstellar space[1]. Among the numerous complexes that have become known so far, the non-classical halonium radical ions **3** which are accessible by dissociative ionization (electron impact ionization of methyl chloro- or bromoacetate)[2] deserve special attention, since they exhibit unusual structural features. According to ab initio calculations[2b] **3a** can best be described in terms of a complex consisting of the chloromethyl radical **4** and a methyl cation **5**, whereby the electrophile **5** interacts with a non-bonding electron pair of the halogen atom of **4**. In the complex **3a** the spin is localized predominantly on C-1 (0.98 electrons), whereas the positive charge is distributed mainly over C-2 and its hydrogen periphery. The two C–Cl bonds are unequal: C^1–Cl (1.76 Å, 6-31G*) is about 0.1 Å shorter than C^2–Cl.

1 **2**

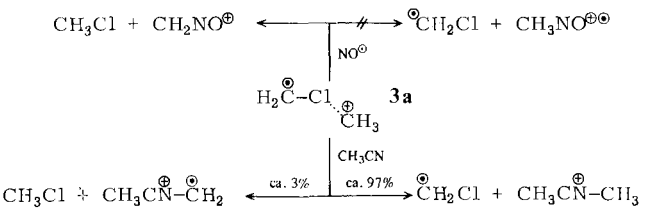
X: Halogen, OH, OAlkyl, SH, NH_2, PH_2
R^1, R^2: H, Alkyl, Halogen
R^3: H, Alkyl



3a, X = Cl
3b, X = Br

4 **5** **3a**

The description of **3** as an ion/dipole complex would suggest that **3** undergoes well-defined reactions with nucleophiles and electrophiles in ion/molecule reactions. The $CH_3^{\oplus}$ ion should be transferred preferably to nucleophiles, the $CH_2^{\oplus\odot}$ radical cation to electrophiles. This prediction is confirmed neatly in a Fourier transform ion cyclotron resonance (FT-ICR) experiment[3]: At reaction times of $t = 1.5$ s CH_3CN extracts from **3a** a $CH_3^{\oplus}$ ion for ~97% and a $CH_2^{\oplus\odot}$ group for only ~3%; the electrophile $NO^{\odot}$, on the other hand, induces exclusively $CH_2^{\oplus\odot}$ transfer (Scheme 1). Similar product ratios are found when one extrapolates to $t = 0$. A completely analogous reactivity is shown by **3b**, which transfers a $CH_3^{\oplus}$ group to CH_3CN to the extent of ~95% (ca. 5% transfer of $CH_2^{\oplus\odot}$), but only the $CH_2^{\oplus\odot}$ radical cation to $NO^{\odot}$[4].



Scheme 1.

$NO^{\odot}$ also reacts to a slight extent with $C_2H_5X^{\oplus\odot}$ (X = Cl, Br) by electron transfer to give $NO^{\oplus}$; we assume, however, that **3** does not participate in this reaction, but rather the isomer $CH_3CH_2X^{\oplus\odot}$, which could be formed by thermolysis of the acetate in the proximity of the hot fila-

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ment, and subsequent ionization. This interpretation is supported by the observation that the molecular ion generated by direct ionization of CH_3CH_2X (X = Cl, Br) reacts with $NO^{\odot}$ exclusively by electron transfer. Thermally induced processes could also be responsible for the $C_2H_5X^{\oplus\odot}$ ions (X = Cl, Br) generated from the esters transferring a proton to CH_3CN, a reaction which also occurs in the case of the directly generated $CH_3CH_2X^{\oplus\odot}$ species.

Preliminary investigations on the ion/dipole complex $H_2\overset{\odot}{C}-\overset{\oplus}{X}H$ (X = Cl, Br) revealed that its reactivity corresponds completely to that of its higher homologs **3**. **6** reacts with bases such as CH_3CN, CH_2O, H_2O or CF_2O by proton transfer from the X–H group, whereas $CH_2^{\oplus\odot}$ transfer takes place in the reaction with $NO^{\odot}$.

Experimental

The FT-ICR studies were carried out on a home-built FT-ICR mass spectrometer [3a, b] under the following conditions [3c, d]: Total pressure 10^{-4}–10^{-5} Pa (same partial pressures of the individual components in each case). In a typical experiment positive ions were generated by an electron beam pulse (pulse duration 5 ms, energy 15 eV, emission current 500 nA). Positive ions were trapped in the cubic ICR cell (15.6 cm^3) at a magnetic field of 1.4 T by application of a small positive potential (+1 V) to the trapping plates. The ions to be investigated were isolated first by creation of a notch in the wave-form of the excitation pulse [3e, f] and then their reactions with the neutral molecules were studied.

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[4] The structures of the product ions depicted in Scheme 1 have not been determined unequivocally.

Iron Clusters with Coupled Phosphido-Phosphane Bridges**

By *David J. Brauer, Sibbele Hietkamp, Herbert Sommer,* and *Othmar Stelzer**

Ditertiary phosphanes $R_2P-CH_2-PR_2$ are able to bridge metal-metal bonds to form an M_2P_2C five-membered ring (**A**)[1]. Until now, no example of ring systems of this type or of chain-like complexes **B**[2] were known with the PH-functional ligands R_2P-CH_2-PRH and $RHP-CH_2-PRH$. Both binuclear complexes are of interest for the synthesis of ligand-stabilized clusters since the $H-P-CH_2-P$ skeleton can insert a third metal atom between P and H to form **C**. The small distance of the metal atoms in **C** favors their linkage to afford cluster **D**.

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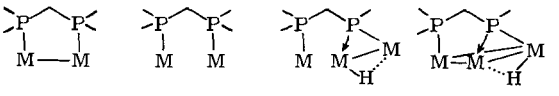
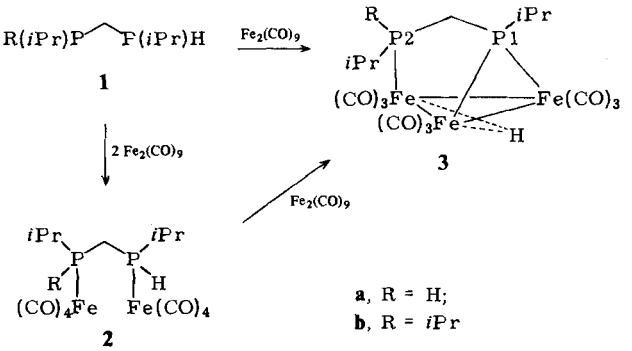
[**] Linear Oligophosphaalkanes, Part 8.—This work was supported by the Fonds der Chemischen Industrie and by the Deutsche Forschungsgemeinschaft.—Part 7: H. Sommer, S. Hietkamp, O. Stelzer, *Chem. Ber.*, in press.

The phosphido-phosphane group $RR'P-CH_2-PR$ (R' = R, H) is a novel bridging unit for trinuclear clusters **D**, and is functionally related to other known μ_3-ligands[3].



Clusters **3a** and **3b** (type **D**) (see Table 1) are formed spontaneously when ligands **1a** and **1b**[4], respectively, are allowed to react with $Fe_2(CO)_9$ in a molar ratio of 1:6. As intermediates the orange, binuclear metal complexes **2a** and **2b** (type **B**) can be isolated[5].



3a and **3b** (intense violet) exhibit $^{31}P\{^1H\}$-NMR spectra (32.2 MHz, 85% H_3PO_4 ext.) of type AB with chemical shifts and coupling constants for the P–C–P system typical of μ_2-phosphido and Fe–P(*i*Pr)R groups (R = H, *i*Pr): δP2 **3a**: 37.8, **3b**: 55.2; δP(1) **3a**: 201.2, **3b**: 189.5, ^2J(PP) **3a**: 86.5, **3b**: 79.2 Hz. The ^{1}H-NMR signals for the H atoms bonded to Fe at $\delta = -19.3$ (**3a**) and -22.5 (**3b**) are split into doublets of doublets by coupling to the phosphorus atoms 1 and 2. J(PH) **3a**: 47.6, 8.9, **3b**: 28.0, 17.5 Hz. In the $^{13}C\{^1H\}$-NMR spectra of **3a** and **3b**, asymmetry and pseudoasymmetry effects lead to doubling of the number of lines for the Me groups of the *i*Pr substituents on P1 (Table 1).

Table 1. $^{13}C\{^1H\}$-NMR spectra of **3a** and **3b**, δ-values (20.0 MHz, CD_2Cl_2, TMS int.). Coupling constants [Hz] in parenthesis; (A) and (B) refer to the *i*Pr groups at P2 and P1, respectively.

CH_3	CH	CH_2	CO
3a			
21.5 (A) 7.4)	27.6 (A)	40.5	210.2 (20.6, 1.7)
19.6 (A) (1)	(24.6, 8.5)	(14.6, 13.9)	209.4 (25.3, 2.2)
20.5 (B) (4.6)	26.7 (B)		216.9 (47.2, 14.1)
20.4 (B) (4.7)	(20.4, 17.6)		211.9 [a]
3b			
18.9 (A) (1.0)	28.7 (A)	24.6	214 [b]
18.6 (A) (1.8)	(13.5, 4.8)	(19.8, 11.3)	213 [b]
21.2 (B) (3.6)	37.9 (B)		
	(17.7, 12.0)		

[a] Broad signal, intensity ratio of signals ca. 6:1:1:1. [b] Overlap of several signals.

In accord with the proposed structures, no bands for CO bridges are observed in the IR spectra of **2** and **3**[6]. The crystal structure analysis[7] of **3b** confirms the presence of the Fe_3P_2C skeleton. The Fe atoms form a triangle whose

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shortest edge is bridged by the phosphido group $-CH_2(iPr)P$. The H-bridge between the iron atoms 2 and 3 lengthens the Fe2–Fe3 bond (Fig. 1). As a two-electron,

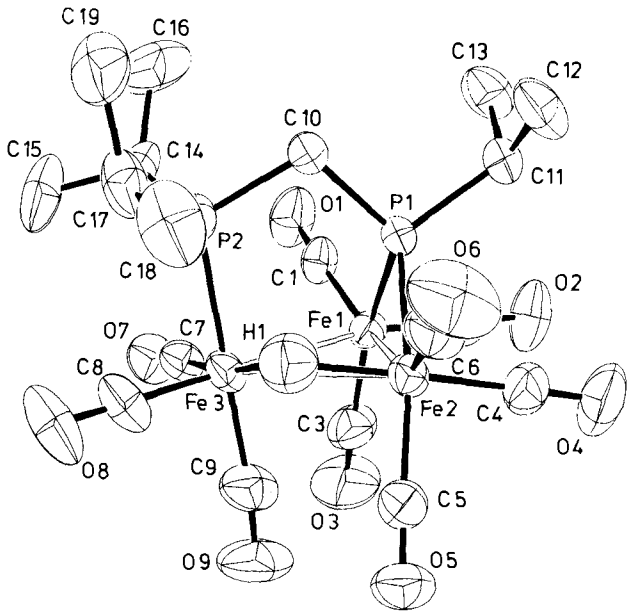

Fig. 1. Structure of **3b** in the crystal. Selected bond lengths [Å]: Fe1–Fe2 2.6994(7), Fe1–Fe3 2.7300(7), Fe2–Fe3 2.7993(7), P1–Fe1 2.1779(8), P1–Fe2 2.194(1), P2–Fe3 2.293(1), H1–Fe2 1.70(5), H1–Fe3 1.59(5); selected bond angles [°]: P1–C10–P2 107.0(2), Fe1–P1–Fe2 76.26(3), Fe2–H1–Fe3 117(3).

three-center bond, the Fe–(H)–Fe system is similar to that in the isoelectronic $Os_3(CO)_{11}H_2$[8]. Reaction of the intermediate **2** with other carbonylmetal compounds should also facilitate the synthesis of heterometal clusters with the RR'P–CH_2–PR bridge, which functions as a [2+3]-electron donor.

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CAS Registry numbers:
2a, 89869-55-6; **2b**, 89869-60-3; **3a**, 91239-46-2; **3b**, 91239-47-3; $Fe_2(CO)_9$, 15321-51-4.

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[5] Procedure: **1b** (0.69 g, 3.35 mmol) is added over 20 min to a suspension of $Fe_2(CO)_9$ (7.30 g, 20.1 mmol) in 100 mL *n*-octane and heated to 65°C. The intense violet reaction mixture is filtered off and cooled to 0°C. Deep violet crystals of **3b** (1.2 g, 57.4%) precipitate. **3b** is recrystallized from petroleum ether (40/60) at 0°C.
[6] IR (n-hexane): **2a**: 2059, 2054, 1983, 1962, 1945, 1933; **2b**: 2056, 1989, 1967, 1956, 1943; **3a**: 2069, 2032, 2008, 1994, 1984, 1970, 1957; **3b**: 2068, 2051, 2022, 2009, 1988, 1976, 1962 cm^{-1}.
[7] Monoclinic, $P2_1/c$, $a = 8.858(3)$, $b = 16.391(6)$, $c = 18.526$ Å, $\beta \approx 104.22(2)°$, $V = 2607.6$ Å^3, $\rho_{calc} = 1.594$ g/cm^3; $Mo_{K\alpha}$, 4037 independent reflections, $R = 0.034$ for 3128 observed reflections ($|F_o| > 4\sigma(|F_o|)$) and 312 parameters, $R_w = 0.041$ ($w = 1/\sigma^2(|F_o|)$).—Further details on the crystal structure investigation can be obtained from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, by quoting the depository number CSD 50842, the names of the authors, and the journal citation.
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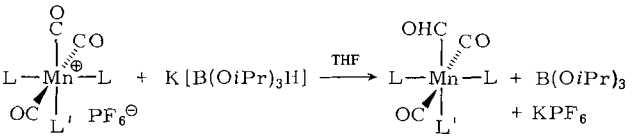
Stable Formylmanganese Complexes**

By *Heinz Berke**, *Gottfried Huttner*, *Olaf Scheidsteger*, and *Gertrud Weiler*

Formyl complexes have been postulated as intermediates in catalytic cycles leading to homogeneous hydrogenation of CO[1–3]. Until now, only neutral η^1-formyl complexes of heavy transition metals could be isolated[4–7]; neutral formyl compounds of 3d metals are particularly unstable and have been detected only by spectroscopy[8,9]. The prototype of this type of complex, $(OC)_5MnCHO$, has not yet been prepared[10]. We therefore wished to investigate whether a modification of the ligand sphere, e.g. substitution of carbon monoxide by phosphite ligands, stabilizes formyl complexes of this type.

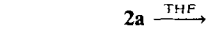
Reaction of the salts of the *trans*-diphosphite- or *mer*-triphosphite-substituted carbonylmanganese cations **1**[11] with potassium hydro(triisopropoxoborate) in tetrahydrofuran (THF) leads to high yields of the isolable formyl complexes **2**[12].



1 **2**

a, L = $P(OPh)_3$, L' = CO; **b**, L = $P(o\text{-}OC_6H_4CH_3)_3$, L' = CO; **c**, L = L' = $P(OPh)_3$

The IR and ^{1}H-NMR spectroscopic data for **2** are consistent with the constitution proposed[13]. The novel formyl complexes are stable; **2a** undergoes decarbonylation above 56°C via a 1st order reaction ($k = 2.12 \times 10^{-4}$ s^{-1}):



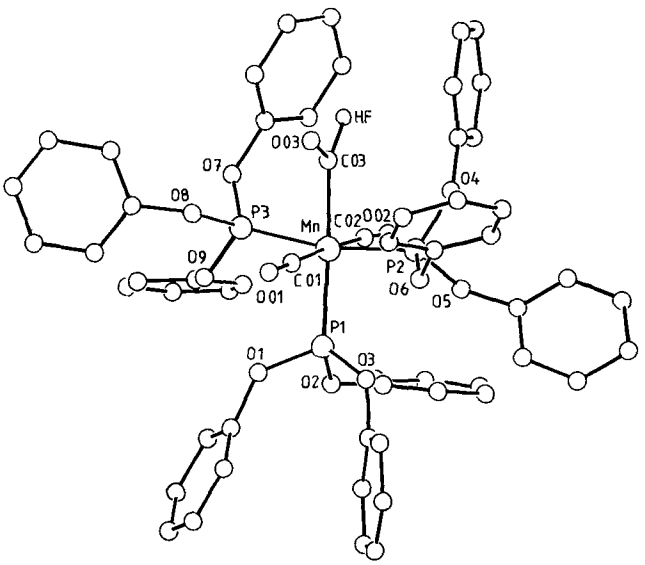


Fig. 1. Structure of **2c** in the crystal. Selected bond lengths [pm] and angles [°]: Mn-C03 204(1), C03-O03 121(1), C03-HF 120, Mn-P1,P2,P3 220.7(3), 220.2(3), 219.7(3); Mn-C02-O03 126.5(5), Mn-C03-HF 131.3, P2-Mn-P3 168.8(1), P1-Mn-P2 94.3(1), P1-Mn-P3 96.8(1), C01-Mn-C02 177.3(2).

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The isotope effect ($k_H/k_D = 3.24$) indicates that rupture of the $(C-H)_{formyl}$ bond is rate-determining for the elimination of CO.

X-ray structure analysis of **2c**[14] showed that the Mn atom is almost octahedrally coordinated (Fig. 1). P2 and P3 are displaced slightly towards the formyl group, which in turn is strongly shielded by the phenyl rings of the phosphite ligands. The formyl groups and Mn, CO1, CO2 as well as P1 are coplanar and hence an optimal π-acceptor bond to the formyl ligand arises. The Mn–CO3 bond is ca. 10 pm shorter than the Mn-alkyl[15], but approximately the same length as the Mn-acyl bonds in neutral complexes[16]. The $(C-O)_{formyl}$ bond lengths and $(Mn-C-O)_{formyl}$ bond angles are largely consistent with those in $CpRe(NO)(PPh_3)CHO$[5].

Aryl phosphite ligands can therefore sterically and electronically stabilize formyl complexes of 3d metals. The degree of stabilization depends on the type and arrangement of the ligands in the complex.

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[7] C. P. Casey, M. A. Andrews, D. R. McAlister, J. E. Rinz, *J. Am. Chem. Soc. 102* (1980) 1927.
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[12] A solution of **1** (1 mmol) in anhydrous tetrahydrofuran (THF) at −80°C is treated with 1 mL of a 1 M solution of $KHB(O\text{-}iPr)_3$ in THF and warmed rapidly to 20°C. The solvent is removed in vacuo and the residue taken up in toluene. The insoluble fraction is filtered off over silica gel under an inert gas atmosphere, and, after concentration of the filtrate, petroleum ether added until onset of precipitation. **2** is obtained as pale yellow crystals at −40°C in 80–90% yield.
[13] **2a**: IR (CH_2Cl_2): $\nu = 2020$ (w), 1970 (vs), 1950 (s), 1580 (s) cm^{-1} (CO); ^{1}H-NMR (CD_3COCD_3, rel. TMS, −30°C), $\delta = 14.19$ (s, CHO), 7.05–7.40 (m, C_6H_5).—**2b**: IR (CH_2Cl_2): $\nu = 2030$ (w), 1970 (vs), 1950 (s), 1600 (s) cm^{-1} (CO); ^{1}H-NMR ($CDCl_3$, rel. TMS, −30°C), $\delta = 14.12$ (s, CHO), 7.0–7.3 (m, C_6H_5), 2.16 (s, CH_3).—**2c**: IR (CH_2Cl_2): $\nu = 1970$ (w), 1932 (s), 1585 (s) cm^{-1} (CO); ^{1}H-NMR (C_6D_6, rel. TMS, 35°C), $\delta = 14.48$ (d, t, $J(PH) = 24/4$ Hz, CHO), 6.68–7.2 (m, C_6H_5).
[14] Pale yellow crystals by diffusion from pentane into a solution of **2c** in toluene. $a = 1201.2(8)$, $b = 2359(2)$, $c = 2231(2)$ pm, $\beta = 127.89(5)°$, $V = 4987.7 \times 10^6$ pm^3, space group $P2_1/c$, $Z = 4$, $F_{000} = 2216$, $\rho_{calc} = 1.43$ g/cm^3, $\mu(Mo_{K\alpha}) = 4.4$ cm^{-1}, $Mo_{K\alpha}$, graphite monochromator, ω-scan ($\Delta\omega = 1.1°$, $2.2 \leq \omega \leq 29.3°$ min^{-1}, $1° \leq 2\theta \leq 45°$), $T = -60$°C, 4360 reflections ($I \geq 2\sigma$). Solution of structure: direct methods (SHELXTL), solution in $P2_1$ subcells, transformation of all heavy atoms according to $P2_1/c$. Mn, all CO ligands, P, and all other O atoms refined anisotropically, H atoms partly found (HF), partly calculated from ideal geometry (388 variables). $R_1 = 0.063$, $R_2 = 0.069$. Further details of the crystal structure analysis can be obtained from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, by quoting the depository number CSD 50879, the names of the authors, and the journal citation.
[15] J. Engelbrecht, T. Greiser, E. Weiss, *J. Organomet. Chem. 204* (1981) 79; M. A. Bennett, G. B. Robertson, R. Watt, P. O. Whimp, *J. Chem. Soc. Chem. Commun. 1971*, 752.
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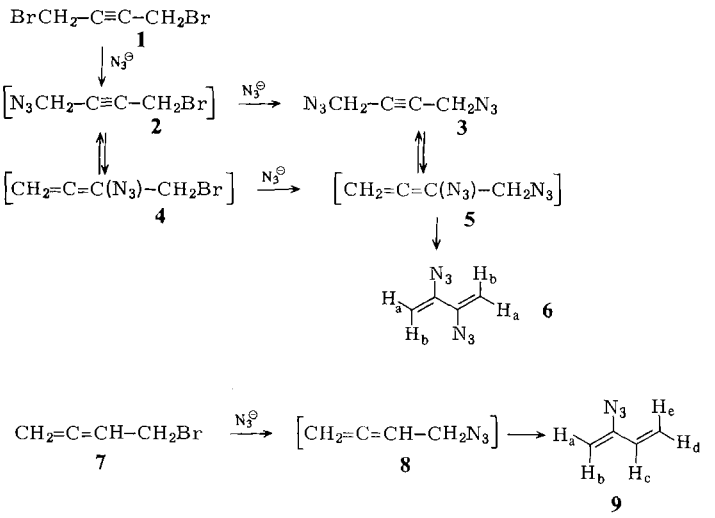
Synthesis of Azidobutadienes**

By *Hanno Priebe**

Unsaturated azides have attracted increasing attention as intermediates in recent years. In the case of vinyl azides the spectrum of reaction covers thermolyses, photolyses, cycloadditions, as well as nucleophilic and electrophilic additions[1]. They are prepared by halogenoazide addition to an olefin and subsequent hydrogen halide elimination[2]. Herein, a convenient route to azidobutadienes is described; for the first time, a N_3-group is directed, via allyl rearrangement, into a vinyl position. Hitherto, only allyl rearrangements in propene and butene systems were known, in which the N_3-group migrates from one allyl position to another[3].



1,4-Dibromo-2-butyne **1** reacts in aqueous ethanolic sodium azide solution with initial formation of 1,4-diazido-2-butyne **3**[4]. When solutions of **3** in benzene, chloroform, or aqueous acetone are heated to 40–70°C, 2,3-diazido-1,3-butadiene **6** is formed. The rate of formation of **6** from **3** was measured NMR spectroscopically between 25 and 70°C[5]. The activation parameters of this first-order reaction are listed in Table 1.

Table 1. Activation parameters of the rearrangement **3** → **6**.

Solvent	lg*A*	E_a [kJ]	$\Delta H^{\ddagger}_{298}$ [kJ]	$\Delta S^{\ddagger}_{298}$ [J/mol K]
70% [D$_6$]acetone/D_2O	8.88	84.82	82.35	−82.90
$CDCl_3$	8.86	85.45	82.98	−83.32
C_6D_6	8.07	80.18	77.71	−98.39

In aqueous acetone, no products were obtained which could have been formed in an ionic reaction. The polarity of the solvent has very little, if any, influence on the rate of the reaction. The negative activation entropy is indicative of an ordered transition state. This means that the two N_3-groups in **3** migrate one after the other in intramolecular

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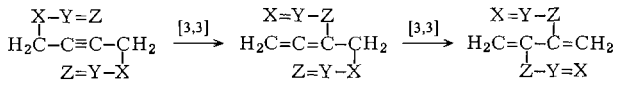
[**] Organic Azides, Part 4. This work was supported by the Royal Norwegian Council for Scientific and Industrial Research.—Part 3: [4].

reactions to give **6** via intermediacy of 3,4-diazido-1,2-butadiene **5**. The diazide **6** can be most simply prepared in a one-pot reaction by heating **1**[6a] in an aqueous ethanolic solution of sodium azide[7]. In principle, the reaction can proceed both via the diazide **3** as well as via 3-azido-4-bromo-1,2-butadiene **4**. Both reaction paths lead to the diazide **5**. Neither 1-azido-4-bromo-2-butyne **2** nor the compounds **4** and **5** could be isolated.

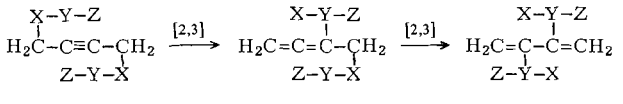
On allowing an aqueous methanolic sodium azide solution of 4-bromo-1,2-butadiene **7**[6b] to stand for 5 d, complete conversion into 2-azido-1,3-butadiene **9** takes place. **9** is most conveniently prepared by reaction of **7** with tetramethylguanidinium azide[8] in sulfolane. The postulated intermediate 4-azido-1,2-butadiene **8** could not be isolated; apparently it rapidly rearranges to the vinyl azide **9**.

The reaction **3**→**6** is a hetero-Claisen rearrangement (Scheme 1); this rearrangement is also known in the case of the hydrocarbon analogue (XYZ = $-CH_2-CH=CH_2$).



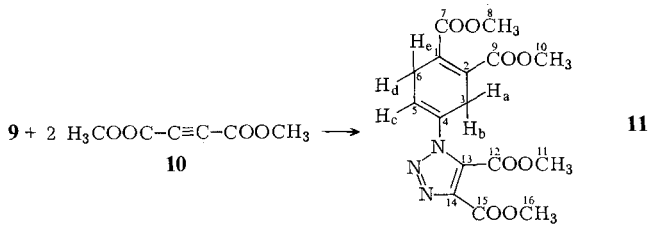
Scheme 1. XYZ = N_3.

A related reaction is the sulfenate ester rearrangement (Scheme 2)[14]. Such reactions open up a convenient entry to 2,3-disubstituted 1,3-butadienes.



Scheme 2. XYZ = −O−S−Ph.

Since dimethyl acetylenedicarboxylate **10** reacts with azides to give 1,2,3-triazoles and with 1,3-butadienes to give 1,4-cyclohexadienes[10], the azides **6** and **9** were allowed to react with this reagent (Scheme 3). On allowing an etheral solution of the monoazide **9** and the dienophile



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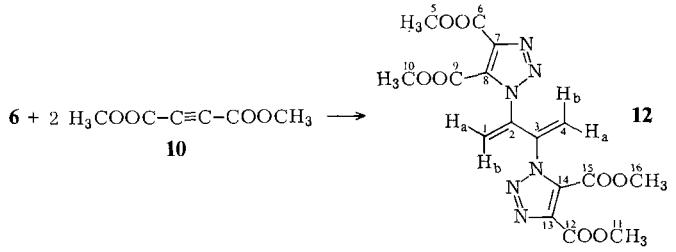

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Scheme 3. Reaction of the azides **6** and **9** with dimethyl acetylenedicarboxylate **10** to give the adducts **11** and **12** [11, 12], respectively. Arbitrary numbering for assignment of the ^{13}C-NMR data.

10 (excess) to stand at room temperature for 6 months, the bisadduct **11** crystallized out[11]. Under the same conditions, the diazide **6** likewise only adds two equivalents of **10**; in the product **12**, the butadiene moiety is *trans*-configurated, thus hindering a Diels-Alder reaction.

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CAS Registry numbers:
1, 2219-66-1; **2**, 91686-82-7; **3**, 91686-83-8; **4**, 91686-84-9; **5**, 91686-85-0; **6**, 91686-86-1; **7**, 18668-68-3; **8**, 91686-87-2; **9**, 91686-88-3; **10**, 762-42-5; **11**, 91686-89-4; **12**, 91686-90-7.

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[4] H. Priebe, *Acta Chem. Scand. B*, in press.

[5] a) **3**: ^{1}H-NMR (200 MHz, $CDCl_3$): $\delta = 4.00$ (s); b) **6**: ^{1}H-NMR ($CDCl_3$): $\delta = 5.40$ (d, $J_{ab} = 1.63$ Hz, $2H_a$), 4.88 (d, $2H_b$); ^{13}C-NMR (50.3 MHz, $CDCl_3$): $\delta = 139.00$ (C-2, C-3), 99.50 (C-1, C-4); IR (film): $\nu = 3034$, 2151, 2098, 1575, 1375, 1273, 856 cm^{-1}; UV (CH_3CN): $\lambda_{max} = 221$ nm ($\lg\varepsilon = 3.94$), 247 (3.92); MS (70 eV): *m/z* (% rel. Int.) = 136 ($M^{\oplus}$, 9), 53 (13), 40 (100).

[6] a) L. Brandsma, H. D. Verkruijsse: *Synthesis of Acetylenes, Allenes and Cumulenes*, Elsevier, Amsterdam 1981, p. 221; b) *ibid.*, p. 188.

[7] *All the azides described here are explosive and therefore should only be handled under the strictest safety precautions!* **6**: A solution of **1** (2.5 mL, 23.5 mmol) and sodium azide (6.1 g, 94 mmol) in 33 mL water and 100 mL ethanol was heated for 18 h at 50°C. Ethanol, together with **6**, was distilled from the mixture under a water-jet vacuum. This solution was diluted with 50 mL water and stored for ca. 15 h at −25°C. **6** (1.7 g, 53%) crystallized out as colorless, light-sensitive needles having a penetrating odor, and which could be sublimed at 25°C/20 torr; m.p. 33°C.

[8] A. J. Papa, *J. Org. Chem. 31* (1966) 1426.

[9] **7** (4.0 g, 30 mmol) was added dropwise to a solution of tetramethylguanidinium azide (15.8 g, 0.1 mol) in sulfolane (100 mL) and the mixture heated at 55–60°C for 1.5 h. The product was sucked into a cold-trap (−196°C) under oil-pump vacuum and recondensed subsequently, it could be dried by passage through a U-tube filled with P_4O_{10}. **9** (2.5 g, 90%) was obtained as a yellow liquid, b.p. 74°C/760 torr (extrapolated), $[\alpha]_D^{20} = 1.4826$; ^{1}H-NMR ($CDCl_3$): $\delta = 6.17$ (ddd, $J_{a(b)c} = 0.35$ Hz, $J_{ce} = 17.00$, $J_{cd} = 10.56$, H_c), 5.52 (m, H_e), 5.16 (m, H_d), 4.97 (m, H_a), 4.86 (m, H_b); ^{13}C-NMR ($CDCl_3$): $\delta = 140.05$ (C-2), 131.80 (C-3), 116.47 (C-4), 101.39 (C-1); IR (gas): $\nu = 3116$, 3037, 2156, 2121, 1595, 1585, 1380, 1306, 1227, 981, 928, 841 cm^{-1}; UV (CH_3CN): $\lambda_{max} = 219$ nm ($\lg\varepsilon = 4.172$), 247 (3.848); MS (70 eV): *m/z* (% rel. int.) = 95 ($M^{\oplus}$, 25), 67 (10), 50 (5), 41 (100), 40 (14), 39 (18).

[10] a) S. K. Khetan, M. V. George, *Can. J. Chem. 45* (1967) 1993; b) V. S. Miklashevskaja, A. A. Petrov, *Zh. Obshch. Khim. 28* (1958) 1125; *Chem. Abstr. 52* (1958) 20027a; c) N. P. Sopov, V. S. Miklashevskaja, *Zh. Obshch. Khim. 26* (1956) 1914; *Chem. Abstr. 51* (1957) 4968a.

[11] Dimethyl-1-[4,5-bis(methoxycarbonyl)-1,4-cyclohexadienyl]-1,2,3-triazole-4,5-dicarboxylate **11**: A solution of **9** (1.0 g, 10 mmol) and **10** (4.0 g, 28 mmol) in 400 mL ether was allowed to stand for 2 months at 0°C and 4 months at room temperature. The precipitate which separated out was recrystallized from chloroform/ether and afforded **11** (1.0 g, 28%) as colorless crystals, m.p. 115°C. Correct element analysis (C,H,N); ^{1}H-NMR ($CDCl_3$): $\delta = 6.07$ (dddd, $J_{ac} = 3.63$ Hz, $J_{bc} = 1.73$ Hz, $J_{cd} = 1.49$ Hz, $J_{ce} = 3.59$ Hz, H_c), 4.00 (s, 3H, $-OCH_3$(triazole)), 3.98 (s, 3H, $-OCH_3$(triazole)), 3.83 (s, 3H, $-OCH_3$), 3.81 (s, 3H, $-OCH_3$), 3.59 (ddd, $J_{ab} = -8.21$ Hz, $J_{be} = 1.86$ Hz, H_b), 3.55 (ddd, $J_{ad} = 1.21$ Hz, $J_{de} = -8.14$ Hz, H_d), 3.36 (ddd, H_a), 3.31 (ddd, H_e); ^{13}C-NMR ($CDCl_3$): $\delta = 167.54$ (C-9), 166.44 (C-7), 160.02 (C-12), 159.23 (C-15), 138.43 (C-14), 132.26 (C-4), 131.67 (C-13), 130.89 (C-2), 130.03 (C-1), 121.50 (C-5), 53.98 (C-11), 52.73 (C-16), 52.59 (C-8, C-10), 29.97 (C-3), 28.68 (C-6); IR (KBr): $\nu = 3010$, 2955, 1746, 1723, 1656, 1567, 1260, 1043, 823 cm^{-1}; UV (CH_3CN): $\lambda_{max} = 218$ nm ($\lg\varepsilon = 3.98$); MS (70 eV): *m/z* (% rel. int.) = 379 ($M^{\oplus}$, 4), 260 (100), 201 (28), 163 (30), 59 (73).

[12] Tetramethyl-1,1'-[bis(methylene)ethylene]bis(1,2,3-triazole-4,5-dicarboxylate) **12**: A solution of **6** (4.6 g, 33 mmol) and **10** (14.2 g, 0.1 mmol) in 100 mL ether was allowed to stand for 6 months at 0°C. The precipitate which separated out was recrystallized from chloroform/ether and furnished **12** (4.9 g, 36%) as yellowish crystals, m.p. 144°C. Correct elemental analysis (C, H, N); ^{1}H-NMR ($CDCl_3$): $\delta = 5.77$ (d, $J_{ab} = 1.98$ Hz, $2H_b$),

5.43 (d, $2H_a$), 4.02 (s, 6H, $-OCH_3$), 4.00 (s, 6H, $-OCH_3$); ^{13}C-NMR ($CDCl_3$): δ = 159.73 (C-9, C-15), 158.06 (C-6, C-12), 138.86 (C-8, C-14), 136.75 (C-2, C-3), 132.87 (C-7, C-13), 119.93 (C-1, C-4), 54.07 (C-10, C-16), 52.90 (C-5, C-11); IR (KBr): ν = 3120, 2955, 1735, 1604, 1558, 1448, 1220, 953, 557 cm^{-1}; UV (CH_3CN): λ_{max} = 220 nm (lgε = 4.135); MS (70 eV): *m/z* (% rel. int.) = 420 ($M^{\oplus}$, 24), 361 (24), 302 (20), 236 (12), 154 (73), 59 (100).

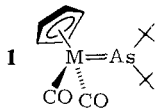
[13] H. Hopf, private communication.

[14] a) S. Jeganathan, W. H. Okamura, *Tetrahedron Lett. 23* (1982) 4763; b) A. J. Bridges, J. W. Fischer, *J. Chem. Soc. Chem. Commun. 1982*, 665.

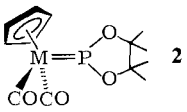
Novel Synthesis of Complexes with Metal-Phosphorus Double Bonds**

By *Elisabeth Gross, Klaus Jörg, Klaus Fiederling, Axel Göttlein, Wolfgang Malisch**, and *Roland Boese*

As recently shown for a series of compounds, transition-metal-substituted phosphanes, arsanes, and stibanes $Cp(CO)_3M-ER_2$ (E = P, As, Sb; M = Cr, Mo, W) can be decarbonylated to $Cp(CO)_2M=ER_2$ complexes[1,2]. However, the M-E double bonds are only isolable provided that are protected by bulky ligands R[3] and CO elimination can be easily induced thermally. In this way, **1a**, **b**[1] and **2a**, **b**[4,5] were obtained, whereas the precursor of **2c** is transformed into a binuclear complex upon decarbonylation[4].



a, M = Mo; **b**, M = W



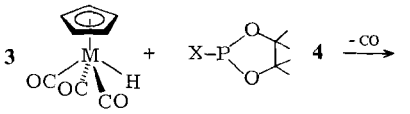
a, M = Cr; **b**, M = Mo; **c**, M = W

Important for the extension of this novel class of compounds are, therefore, mild synthetic methods. One possibility is 1,2-elimination at phosphane complexes having functionalized metal and phosphorus atoms:

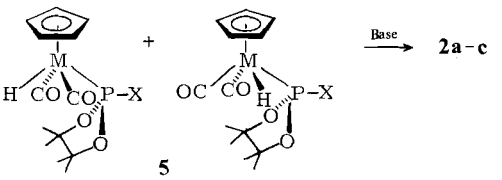
$$M(X)-P(Y) \longrightarrow M=P + XY$$

Ideal precursors are the complexes **5a**—**e**, which can be readily prepared as a mixture of the cis- and trans-isomers by CO substitution from **3a**—**c** and **4a**, **b**. Addition of the base Et_3N or $Me_3P=CH_2$ in benzene at room temperature leads, within minutes, via elimination of HCl or Me_2NH, to **2a**—**c** having an M-P double bond; **2c** could previously not be isolated, and **2c**, **b** are formed in higher yields than via the decarbonylation route[4].

X-ray structure analysis of **2c** (Fig. 1)[7] indicates that the phosphorus atom has trigonal-planar coordination (sum of angles 360°) and that the dioxaphospholane group is arranged perpendicularly to the cyclopentadienyl- and $M(CO)_2$-plane[8]. This orthogonal arrangement was expected, since **2c** is related electronically to the complex ion $[Cp(CO)_2Fe=CR_2]^{\oplus}$, for which theoretical considerations predict this kind of orientation. The W1-P1 distance of 2.181(1) Å is even shorter than the value expected for a W—P double bond (2.26 Å)[9]. A further proof of the sp^2-



a, M = Cr; **b**, M = Mo; **c**, M = W **a**, X = Cl; **b**, X = NMe_2



a, M = Cr, X = Cl; **b**, M = Mo, X = Cl; **c**, M = W, X = Cl; **d**, M = Mo, X = NMe_2; **e**, M = W, X = NMe_2

hybridization of the phosphorus atom in **2c** is provided by the coupling constant J_{PW}, which, relative to that in $Cp(CO)_3W-POCMe_2-CMe_2O$, containing an sp^3-hybridized phosphorus atom increases from 5 to 847 Hz (!). This corresponds to a significant increase in the s-electron density at the phosphorus atom and in the W—P bond.

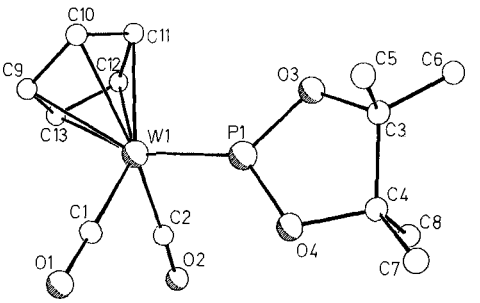


Fig. 1. Structure of **2c** in the crystal. Hydrogen atoms have been omitted for the sake of clarity. Selected bond lengths [Å] and angles [°]: W1-P1 2.181(1), P1-O3 1.619(3), O3-C3 1.458(6); W1-P1-O3 132.3(1), W1-P1-O4 132.6(1), O3-P1-O4 95.1(2), C1-W1-C2 84.7(2). Further details of the crystal structure determination can be obtained from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, by quoting the depository number CSD 50939, the names of the authors, and the journal citation.

The importance of the route to systems with M-P double bonds described here is illustrated by the syntheses of such different complexes as **7** and **9**. A base is required for the double dehydrohalogenation of the binuclear complex **6**, obtained as a 57:40:3-mixture of the *trans/trans*-(sketched), *cis/trans*-, and *cis/cis*-isomers from 3,9-dichloro-2,4,8,10,3,9-tetraoxodiphosphaspiro[5.5]undecane and **3b**. **8a**, **b**, prepared from $(Me_2N)_3P$ and **3b** or $C_5Me_5(CO)_3Mo-H$, reacts in the absence of additional base to afford **9a**, **b** since the starting phosphane itself acts as a bases; **8a**, **b** are therefore only transiently stable in solution.

Preliminary reactions with **9a** indicate that the novel phosphorus-metal double bonds are extraordinarily reac-

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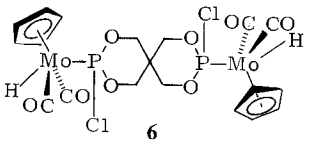
[**] Main-Group Element—Transition Metal Multiple Bonds, Part 6. This work was supported by the Deutsche Forschungsgemeinschaft and by the Fonds der Chemischen Industrie. We thank Dr. *G. Lange* and Dr. *W. Buchner* for the MS and NMR spectra, respectively, and *S. Ammann* for assistance with the experimental work.—Part 5: E. Gross, A. Meyer, W. Malisch, C. Burschka, R. Boese, *J. Chem. Soc. Chem. Commun.*, in press.



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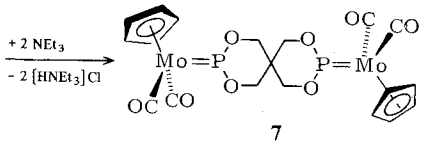

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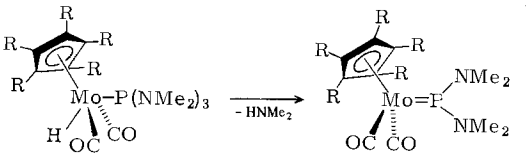
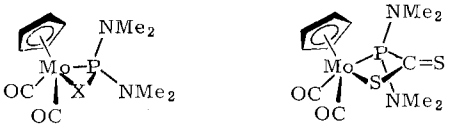


8 9

a, R = H; **b**, R = Me

tive towards S_8, CH_2N_2, $Fe_2(CO)_9$, and CS_2; **10a–c** and **11** are formed. Variable temperature ^{1}H-NMR spectro-



10 11

a, X = S; **b**, X = CH_2; **c**, X = $Fe(CO)_4$

scopic studies on **10a–c** indicate that a rapid "olefin-like" rotation of the $(Me_2N)_2P-X$ moiety occurs[11].

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[1] M. Luksza, S. Himmel, W. Malisch, *Angew. Chem. 95* (1983) 418; *Angew. Chem. Int. Ed. Engl. 22* (1983) 416.

[2] a) K. A. Mahmoud, A. J. Rest, M. Luksza, K. Jörg, W. Malisch, *Organometallics 3* (1984) 501; b) E. Gross, C. Burschka, W. Malisch, *Chem. Ber.*, in press.

[3] This restriction does not apply to the photochemical generation in a CH_4 or N_2 matrix (cf. [2a]).

[4] Decarbonylation of $Cp(CO)_3M-\overline{POCMe_2-CMe_2O}$ in benzene commences at −5 °C (M = Cr, Mo) or 60 °C (M = W) and affords **2a**, **b** (45 and 56%, resp.) or the bridged binuclear complex $(\mu\text{-H})(\mu\text{-}\overline{POCMe_2-CMe_2O})W_2(CO)_4Cp_2$.

[5] For the direct synthesis of the analogous complex $Cp(CO)_2Mo\text{-}\overline{POCH_2-CH_2N}(t\text{Bu})$ from $Na[Mo(CO)_3Cp]$ and $(t\text{Bu})NH_2C-H_2COPCl$ by omission of the **5**-analogue, see L. D. Hutchins, E. N. Duesler, R. T. Paine, *Organometallics 3* (1984) 399, and literature cited therein. For additional complexes with trigonal-planar coordinated phosphorus cf. R. T. Baker, J. F. Whitney, S. S. Wreford, *Organometallics 2* (1983) 1049; H. Lang, L. Zsolnai, G. Huttner, *Angew. Chem. 95* (1983) 1016; *Angew. Chem. Int. Ed. Engl. 22* (1983) 976; *Angew. Chem. Suppl. 1983*, 1451.

[6] Procedure **2c**: A solution of **5c/5e** (669 mg, 1.37 mmol)/(259 mg, 0.52 mmol) and Et_3N (139 mg, 1.37 mmol)/(53 mg, 0.52 mmol) in 30 mL benzene is stirred for 30 min at room temperature. After being filtered, the resulting clear solution is concentrated to 6 mL, whereupon **2c** crystallizes. Yield 478 mg (74%)/122 mg (52%); yellow crystals; m.p. = 165 °C, ^{1}H-NMR (C_6H_6, 60 MHz, 30 °C): δ = 5.17 (s, 5H, H_5C_5), 1.04 (s, 12H, H_3C); ^{31}P[^{1}H]-NMR (C_6D_6, 40.5 MHz, 37 °C): δ = 226.8, $^1J_{^{31}P^{183}W}$ = 847 Hz; IR (C_6H_6): ν(CO) = 1947 vs, 1876 s cm^{-1}; molecular mass 452 (MS relative to ^{184}W).—Yield **2a/b** from **5a/5b** or **5d**: 65/95%. **7/9a/9b** were obtained analogously: yield 34/40/74%; yellow-orange/red/red-brown crystalline powder: m.p. = 124 (decomp.)/98/96 °C; ^{1}H-NMR (C_6H_6, 60 MHz, 30 °C): δ = 4.97 (s, 10H, H_5C_5), 4.74–3.30 (m, 8H, H_2C)/δ = 5.27 (s, 5H, H_5C_5), 2.48 (d, ^3J(HCNP) = 8.5, 12H, H_3CNP)/δ = 2.65 (d, ^3J(HCNP) = 7.8 Hz, 12H, H_3CNP), 2.13 (d, ^4J(HCCMoP) = 1.3 Hz, 15H, H_3CCMo); ^{31}P[^{1}H]-NMR (C_6D_6, 60 MHz, 30 °C) 358.0/142.5/283.5; IR (C_6H_6): ν(CO) = 1943 vs, 1886 s/1918 vs, 1842 s/1925 vs, 1954 s cm^{-1}. Correct elemental analyses were obtained for all compounds.

[7] $\mu Mo_{K\alpha}$-Graphite monochromator, λ = 0.71069 Å, space group $P2_1/n$, Z = 4, a = 13.161(3), b = 7.694(2), c = 15.393(4) Å, β = 106.78(2)°, V = 1492.4(7) Å^3, ρ_x = 2.01 g/cm^3, F_{000} = 864. 2θ:ω-96 step-scan data collection, 3081 independent reflections ($F_o > 3\sigma(F)$), R = 0.042.

[8] B. E. R. Schilling, R. Hoffmann, J. W. Faller, *J. Am. Chem. Soc. 101* (1979) 592.

[9] R. J. Klingler, W. A. Butler, M. D. Curtis, *J. Am. Chem. Soc. 100* (1978) 5034; M. Yoshifuji, I. Sima, N. Inamoto, K. Hirotsu, T. Higuchi, *ibid. 103* (1983) 4587.

[10] W. Malisch, M. Kuhn, *J. Organomet. Chem. 73* (1973) C1.

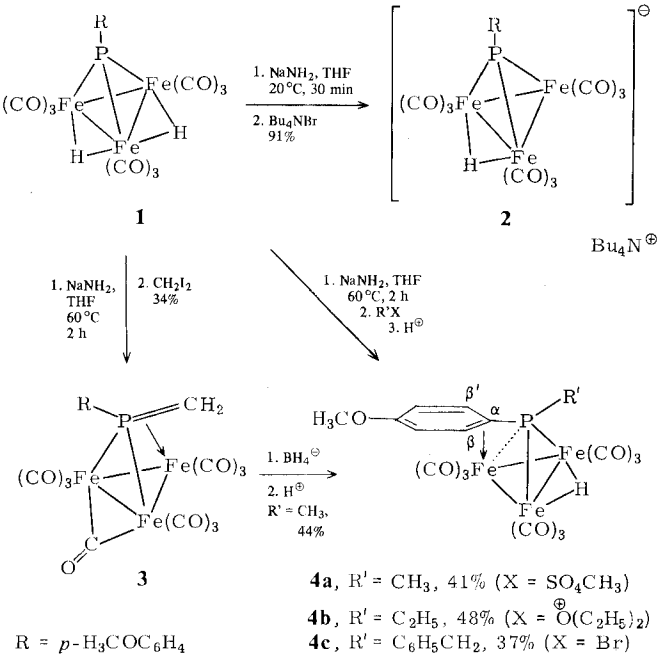
[11] **10a/b/c**: M.p. = 160–161/96–97/168 °C; ΔG^+ [kcal/mol] = 14.2 (T_c = 270)/13.6 (T_c = 251)/14.2 (T_c = 263 °C). **11**: M.p. = 173–174 °C.

Synthesis, Structure, and Reactions of Cluster-Stabilized Phosphaalkenes**

By *Konrad Knoll, Gottfried Huttner*, Marek Wasiucionek,* and *Laszlo Zsolnai*

Phosphanediyl ligands RP are useful groups in neutral clusters forming inert μ_3-bridges which do not interfere in the reactions of the cluster[1]. Herein, we show that after twofold deprotonation the cluster $[(\mu_3\text{-RP})Fe_3(CO)_9(\mu_2\text{-H})_2]$ **1** reacts via the μ_3-RP group with electrophiles. With CH_2I_2, the cluster **3** is formed, in which for the first time a phosphaalkene, $RP{=}CH_2$, is stabilized as a μ_3-η^2 bridge; it can be reduced in the cluster to a novel μ_3-η^3-phosphino ligand $RPCH_3$. The cluster **4** thus formed is also accessible directly from the phosphanediyl complex **1**.

The dihydrido-Fe_3 cluster **1** (R = *p*-$CH_3OC_6H_4$)[2] undergoes deprotonation on reaction with $NaNH_2$; short reaction times lead at 20 °C to the monoanion, which can be



1 **2** **3**

4a, R' = CH_3, 41% (X = SO_4CH_3)
4b, R' = C_2H_5, 48% (X = $\overset{\oplus}{O}(C_2H_5)_2$)
4c, R' = $C_6H_5CH_2$, 37% (X = Br)

R = *p*-$H_3COC_6H_4$

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isolated as the $Bu_4N^{\oplus}$ salt **2**. According to the X-ray structure analysis[3], the tetrahedral skeleton of the anion of **2** closely resembles that of $[(\mu_3\text{-}C_6H_5P)Fe_3(CO)_9(\mu_2\text{-}H)_2]$[2]. The position of the H-bridge could be determined directly; the different Fe–Fe distances (267.8(3), 267.9(2), 271.8(3) pm) also give an indication of the position of the H-atom, which as expected bridges the long bond[2]. The FeP distances (214.3(5), 216.3(3), 216.3(3) pm) are, on average, 1 pm shorter than in $[(\mu_3\text{-}C_6H_5P)Fe_3(CO)_9(\mu_2\text{-}H)_2]$[2].

When **1** is allowed to react with $NaNH_2$ in tetrahydrofuran (THF) at 60 °C for 2 h, a highly air-sensitive substance is formed, which, according to its reactivity and IR spectrum, is a dianion. It differs from the monoanion of **2** in its ν_{CO} absorptions: the ν_{CO} bands of the anion of **2** are, on average, shifted about 55 cm^{-1}, and those of the dianion, about 120 cm^{-1} to longer wavelengths compared to those of **1**. The dianion reacts with CH_2I_2 to give the neutral complex **3**.

One of the PFe bonds in **3** is bridged by a CH_2-group. The loss of the μ_2-H bridges of **1** is electronically compensated for by a μ_2-CO group. The $RP{=}CH_2$ ligand can be regarded as a coordinatively stabilized phosphaalkene. This interpretation is supported by the X-ray structure analysis of **3**[3], which shows a relatively short[4] PC distance (176(1) pm). In free phosphaalkenes the bond is even shorter (168–172 pm)[5]. A similar coordination is observed in reduced nitrile[6a] and isonitrile ligands[6b] in Fe_3 clusters.

The phosphaalkene complex **3** can be hydrogenated in a $H^{\ominus}/H^{\oplus}$ addition sequence ($NaBH_4$, THF, 20 °C, 15 min) to **4a**. **3** splits off a CO group, and the resulting vacant coordination is filled by one of the π bonds of the aryl ligand. This new type of coordination of an alkylarylphosphino ligand was confirmed by a structure analysis of **4c**[3]: FeC_α 235.2(8), FeC_β 286.3(8) pm; $C_{\beta'}$ is not coordinated ($FeC_{\beta'}$ 314.3(8) pm). On steric grounds, the P atom is bonded only to the two Fe atoms which carry the bridge H atom (FeP: 219.9(3), 217.1(3) pm); the distance to the third Fe atom is 252.5(3) pm. The H-bridged FeFe bond with a length of 270.3(3) pm is, as usual, longer than the other two FeFe bonds (265.0(3), 264.7(3) pm). The ^{1}H-NMR spectrum of **4a**, with its A_2B_2 pattern, indicates that the β and β' positions rapidly exchange in solution.

4a–c are more easily accessible from **1** by double deprotonation, alkylation, and protonation. This reaction sequence, like the formation of **3**, shows that μ_3-RP ligands in anionic clusters are nucleophilic centers which enable the synthesis of unusual ligand systems.

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[1] a) G. Huttner, J. Schneider, H. D. Müller, G. Mohr, J. von Seyerl, L. Wohlfahrt, *Angew. Chem. 91* (1979) 82; *Angew. Chem. Int. Ed. Engl. 18* (1979) 77; b) J. Schneider, G. Huttner, *Chem. Ber. 116* (1983) 917.

[2] G. Huttner, J. Schneider, G. Mohr, J. von Seyerl, *J. Organomet. Chem. 191* (1980) 161.

[3] **2**: monoclinic, $P2_1/c$, $a = 1076.4(6)$, $b = 1394.0(8)$, $c = 2858(2)$ pm, $\beta = 118.02(5)°$, $Z = 4$, 3602 reflections, $R_1 = 0.064$; **3**: triclinic, $P\bar{1}$, $a = 823.7(5)$, $b = 993.4(8)$, $c = 1355(1)$ pm, $\alpha = 91.80(6)°$, $\beta = 102.72(5)°$, $\gamma = 86.26(5)°$, $Z = 2$, 2407 reflections, $R_1 = 0.057$; **4c**: triclinic, $P\bar{1}$, $a = 941.1(8)$, $b = 1054(1)$, $c = 1320(1)$ pm, $\alpha = 103.00(7)°$, $\beta = 92.13(7)°$, $\gamma = 76.84(7)°$, $Z = 2$, 2376 reflections, $R_1 = 0.045$. Further details of the crystal structure investigations are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD 50924, the names of the authors, and the journal citation.

[4] PC single bond: 183–184 pm; D. E. C. Corbridge: *The Structural Chemistry of Phosphorus*, Elsevier, Amsterdam 1974, p. 393.

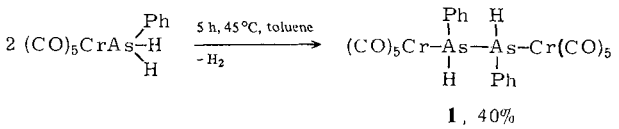
[5] Recent review: R. Appel, F. Knoll, J. Ruppert, *Angew. Chem. 93* (1981) 771; *Angew. Chem. Int. Ed. Engl. 20* (1981) 731, and references cited therein.

[6] a) M. A. Andrews, G. v. Buskirk, C. B. Knobler, H. D. Kaesz, *J. Am. Chem. Soc. 101* (1979) 7245; b) M. I. Bruce, T. W. Hambley, B. K. Nicholson, *J. Chem. Soc. Dalton Trans. 1983*, 2385.

Facile Synthesis of PhAs=AsPh Complexes**

By *Gottfried Huttner** and *Ibrahim Jibril*

Ligands RX=XR (X = P, As, Sb) in which the reactive double bond is protected by side-on coordination[1] are, in contrast to the free ligands[2], stable even for small substituents R. They may be used as sources of molecules with free X=X double bonds[1]. We have now found that the dehydrogenation of complex-bound diarsanes provides a facile and high-yield route to the otherwise difficultly accessible diarsinidene ligands[3].



1, 40%

The diarsane complex **1** is formed on prolonged heating of $(CO)_5Cr(Ph)AsH_2$[4] at 45 °C in toluene. Irradiation, as in the case of the synthesis of $Cp(CO)_2MnPhAs(H)\text{–}(H)AsPhMn(CO)_2Cp$[4] from $Cp(CO)_2MnPhAsH_2$, is not necessary. Reaction of **1** with Pd/C in a molar ratio of 10 : 1 at 20 °C in CH_2Cl_2 leads, within 30 min, to evolution of 1 mol H_2, but the black compounds formed in the reaction, which are soluble in CH_2Cl_2, cannot be separated chromatographically. If, however, equimolar amounts of $P(OMe)_3$ or bpy, the complex

$(CO)_5Cr(Ph)As{=}As(Ph)Cr(CO)_5$ **2**

presumably formed in the initial stage of the reaction, is stabilized as the Pd-derivative **3**.

According to X-ray structure analyses[5], in the complexes **3a** and **3b** the palladium is planar coordinated: two coordination sites are occupied by the donor atoms of the ligand L, the third site by the π-bond of the "arsenobenzene" ligand PhAs=AsPh[6]. The Pd–As distances in **3a** and **3b** are 246(2) and 239(1) pm, respectively. The length of the coordinated As=As bond in **3a** is 236.6 pm and in **3b**, 236.0 pm. The $Cr(CO)_5$ groups bound to the "free electron pair" of the coordinated arsenobenzene ligand show As–Cr distances of 251(3) pm in **3a** and 248(1) pm in **3b**. Thus, the coordination of the RAs=AsR ligand to Pd resembles the coordination of $C_6F_5P{=}PC_6F_5$ to Pt in $(Ph_3P)_2Pt(C_6F_5P{=}PC_6F_5)$[7]. The coordination of the arsenobenzene ligand to three organometallic fragments compares with that in $[(CO)_5M]_3PhX{=}XPh$ (M = Cr, X = P[1a]; M = Cr, X = As[3a]; M = W, X = Sb[8]).

If Pt/C is used instead of Pd/C, the reaction takes a different course, since Pt is not dissolved from the metal under the reaction conditions. Besides cycloarsane com-

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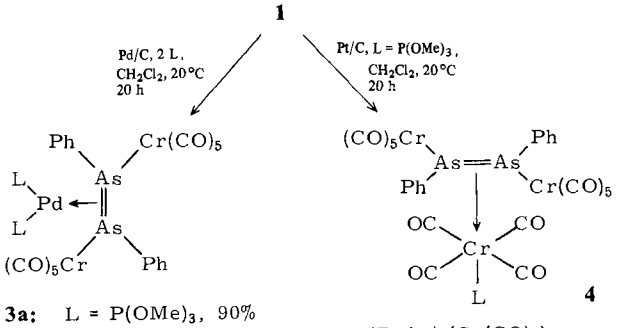
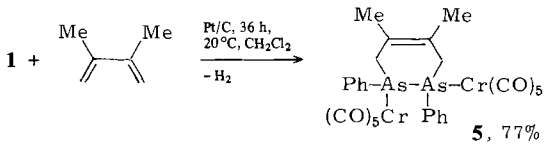


plexes, of which $(PhAs)_5(Cr(CO)_5)_2$ could, as a crystalline substance, be characterized by X-ray structure analysis, complex **4** was obtained, whose structure[5] (As=As 234(1), As–$Cr_{end\text{-}on}$ 249(1), As–$Cr_{side\text{-}on}$ 260(1) pm) compares with that of $((CO)_5Cr)_3PhAs{=}AsPh$[3a]. The substitution of a CO group by $P(OMe)_3$ in the formation of **4** is presumably heterogeneously catalyzed[9]; **2** may be regarded as an intermediate in this reaction too. The following trapping reaction supports this postulation:



5 can be regarded as the product of a [4+2]-cycloaddition of 2,3-dimethylbutadiene to the intermediate **2** initially formed during the dehydrogenation. This is supported not only by the high yields of **5** but also by the observation that the homologous compound $(CO)_5CrPhP{=}PPhCr(CO)_5$ and free ligands RP=PR[10] undergo cycloadditions with cyclopentadiene or 2,3-dimethylbutadiene[1b].

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[1] a) J. Borm, L. Zsolnai, G. Huttner, *Angew. Chem. 95* (1983) 1018; *Angew. Chem. Int. Ed. Engl. 22* (1983) 977; *Angew. Chem. Suppl. 1983*, 1477, and references cited therein. b) G. Huttner, J. Borm, O. Orama, L. Zsolnai, *J. Organomet. Chem.*, in press.

[2] M. Yoshifuji, I. Shima, N. Inamoto, K. Hirotsu, T. Higuchi, *J. Am. Chem. Soc. 103* (1981) 4587; A. H. Cowley, J. G. Lasch, N. C. Norman, M. Pakulski, *ibid. 105* (1983) 5506; C. Couret, J. Escudie, H. Ranaivonjatovo, J. G. Wolf, *Tetrahedron Lett. 24* (1983) 3625; C. Couret, J. Escudie, Y. Madaule, H. Ranaivonjatovo, J. G. Wolf, *ibid. 24* (1983) 2769; C. Couret, J. Escudie, J. Satge, *ibid. 23* (1982) 4941; A. H. Cowley, J. E. Kilduff, S. K. Mehrotra, N. C. Norman, M. Pakulski, *J. Chem. Soc. Chem. Commun. 1983*, 528; A. H. Cowley, J. E. Kilduff, J. G. Lasch, S. K. Mehrotra, N. C. Norman, M. Pakulski, C. A. Stewart, *Phosphorus Sulfur 18* (1983) 3; E. Niecke, R. Rüger, M. Lysek, S. Pohl, W. Schoeller, *Angew. Chem. 95* (1983) 495; *Angew. Chem. Int. Ed. Engl. 22* (1983) 486; *Angew. Chem. Suppl. 1983*, 639.

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[5] **3a**: monoclinic, $P2_1/c$, $a = 1354.1(7)$, $b = 1624(1)$, $c = 2241(2)$ pm, $\beta = 128.97(4)°$, $V = 3832 \times 10^6$ pm^3, $Z = 4$, 3509 independent reflections ($I > 2\sigma$), $R_1 = 0.051$.—**3b**·CH_2Cl_2: monoclinic, $P2_1/c$, $a = 1355(1)$, $b = 1868(9)$, $c = 2221(2)$ pm, $\beta = 131.68(4)°$, $V = 3786 \times 10^6$ pm^3, $Z = 4$, 2389 independent reflections ($I > 2\sigma$), $R_1 = 0.106$.—**4**·CH_2Cl_2: monoclinic, $P2_1/c$, $a = 1655(1)$, $b = 1279.4(7)$, $c = 1935(1)$ pm, $\beta = 108.49(5)°$, $V = 3885 \times 10^6$ pm^3, $Z = 4$, 2835 independent reflections ($I > 2\sigma$), $R_1 = 0.084$. Further details of the crystal structure investigations are available on request from the Fachinformationszentrum, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD 50941, the names of the authors, and the journal citation.

[6] The coordination of Pd in **3** can also be described as distorted square planar.

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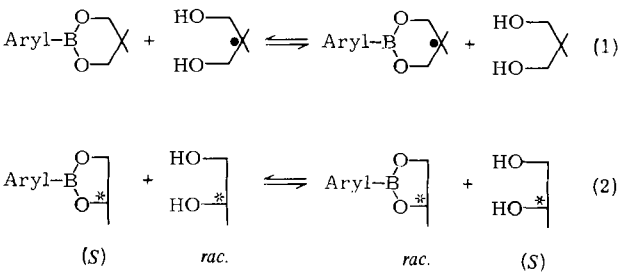
Rapid Proton Transfer as Cause of an Unusually Large Neighboring Group Effect**

By *Günter Wulff**, *Manfred Lauer*, and *Helmut Böhnke*

In connection with our studies on chemoselective affinity chromatography[1], we have investigated the esterification of arylboronic acids with diols in organic solvents. Our aim was to accelerate the establishment of equilibrium in order to make the reaction also useful for very rapid chromatography (HPLC) on polymer bound boronic acid[2]. We recently found[3] that the establishment of equilibrium in the case of *o*-(dimethylaminomethyl)phenylboronic acids is many orders of magnitude faster than in the case of the non-substituted phenylboronic acid. We have now synthesized further compounds[4], which, in some cases, show considerably greater acceleration and from whose structures and reactivities conclusions can be drawn about the mechanism of neighboring group participation.



For investigation of the reactivity, the rate of transesterification in the degenerate equilibria (1) and (2) were measured (see also [3]). In the case of rapid reactions, the rate given in Equation (1) could be determined by dynamic NMR spectroscopy, whereby the coalescence temperatures (T_c) for the methyl groups of the diol moiety were ascertained. Less reactive esters could not be investigated by this method. In these cases the transesterification of the optically active (*S*)-1,2-propanediol esters (ester **b**) with racemic 1,2-propanediol [Eq. (2)] is monitored polarimetrically. The range of measurement by the two methods over-

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laps in the case of the esters **5a** and **5b**, so the values can, to some extent, be correlated (for the evaluation and estimation of the relative rates see [3], footnote 37).

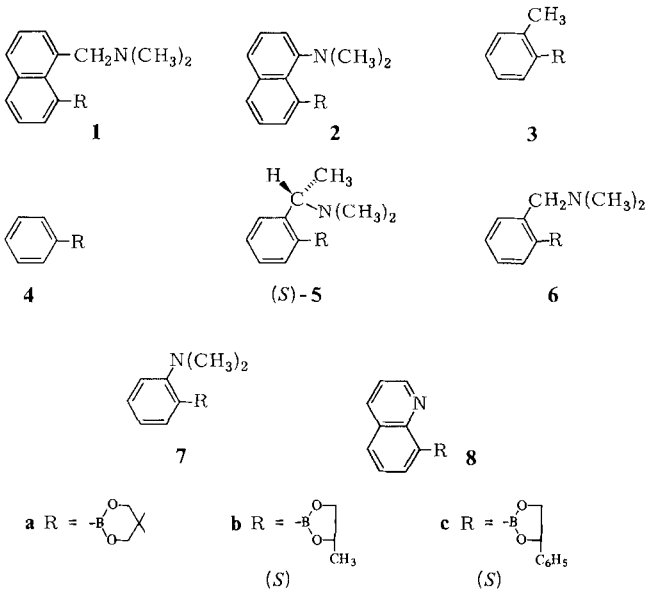


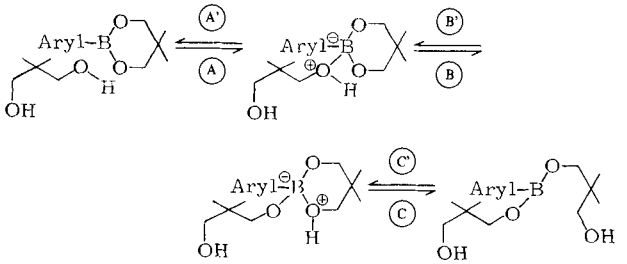
Table 1 shows that differences in reactivity of an unusual order of magnitude occur in similarly structured nitrogen-containing aryl boronates (more than 14 orders of magnitude between **1** and **8**). In the case of compounds **6a**, **7a**, and **8a**, a basic nitrogen atom located at a favorable distance from the boronate ester causes an acceleration of about 8×10^7, 2×10^8 and 4×10^9, respectively, compared to the unsubstituted phenylboronate **4**. The acceleration measured for the quinolineboronates **8a** points to a neighboring group effect of an order of magnitude very rarely met with in other compounds[6].

Table 1. Coordination and ester exchange.

	^{11}B-NMR [a]		$\Delta G_c^{\neq}$ (B–N) [kJ/mol] ($T_c/\Delta\nu$ [°C/Hz]) [b]		Relative rate for transesterifications According to Eq. (2) [c] ($\tau_{1/2}$ [s])	According to Eq. (1) [d] ($T_c/\Delta\nu$ [°C/Hz])
1a	4.9	**1c**	77 (+85/7.2)	**1b**	$\ll10^{-6}$ [f]	–
2a	20.8	**2c**	[e]	**2b**	7×10^{-4} (11000)	–
3a	27.7		–	**3b**	0.03 (240)	–
4a	27.2		–	**4b**	0.13 (62)	–
5a	13.6	**5c**	56 (+4/31)	**5b**	1 (8)	**5a** 1 (+135/13.2)
6a	14.3	**6c**	53 (−32/3.0)		–	**6a** 10^7 (−45/13)
7a	27.9		–		–	**7a** 3×10^7 (−58/11)
8a	28.7		–		–	**8a** 5×10^8 (−85/~21)

[a] ^{11}B-NMR referred to external standard BF_3–$O(C_2H_5)_2$; δ-values. [b] $\Delta G_c^{\neq}$ values for B–N bond breaking determined from the coalescence of the N-methyl groups of ester **c**; T_c = coalescence temperature (methodology see [5]). [c] $\tau_{1/2}$ for the transesterification of the ester **b** determined by polarimetric measurement at 20.0°C (ester **b** and *rac*-1,2-propanediol each 0.01 M in acetone. Methodology see [3]). [d] Coalescence temperatures for the methyl groups of the diol moiety (ester *a* and diol each 0.2 M in acetone. Methodology see [3]). [e] A free rotation of the two substituents is blocked by steric hindrance here, independently of a B–N coordination. [f] Hardly any reaction detectable after 14 d.

The large differences in reactivity cannot be explained in terms of the different degree of hybridization on boron, as is determined by ^{11}B-NMR spectroscopy[7]. In Table 1, sp^2-hybridized esters (**3a**, **4a**, **7a**, **8a**) are readily recognizable alongside those with more or less strong sp^3-hybridization (**2a** < **6a** < **5a** < **1a**). Even in the case of substantial sp^3-hybridization in **6a**, a similarly rapid transesterification occurs as in **7a**: The attack of a nucleophile in **6a** is not significantly hindered by B–N interaction since the equilibrium between forms with closed and open B–N bonding is established very rapidly, as is shown by the low $\Delta G_c^{\neq}$ values (Table 1) for the B–N bond opening. However, in the case of a very tight B–N interaction as in **1b** the primary nucleophilic attack of the alcohol at the boron (step A, Scheme 1) is so firmly blocked that the reaction rate is drastically lowered.



Scheme 1.

The large acceleration in the reaction of **6a**, **7a**, and **8a** is not due to a preceding quick equilibrium caused by the basic amino group with formation of alkoxide, since added amines, such as quinoline, dimethylbenzylamine, dimethylaniline, or triethylamine in the reactions of esters of **3**, have only a slight accelerating effect.

The transesterification reaction (2) of the esters **3b** and **4b** shows, on using diol which is deuterated at the OH groups, a kinetic deuterium isotope effect of $k_H/k_D = 4-5$. Such an isotope effect could not be detected in the case of esters **5a**, **6b**, and **8b**. Therefore, it must be concluded that the proton transfer (step B, Scheme 1) is rate determining in the transesterification of esters **3** and **4**. In the case of esters **6** and **8** (and perhaps also **7**) this proton transfer is apparently accelerated so strongly by a suitably spaced basic grouping that another step (probable C) now becomes the slowest. In the case of esters **1**, step A might be rate determining because of the competition with the B–N bond, in the case of esters **2** and **5**[8] because of steric hindrance.

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Stereoelectronic Effects in Organic Chemistry. By *P. Deslongchamps*. Pergamon Press, Oxford 1983. xi, 375 pp., paperback, £ 15.25.

This book constitutes the first volume of the "Organic Chemistry Series" edited by *J. E. Baldwin*. It is to be welcomed that an author, who has himself made important advances in this area, provides a review of stereoelectronic effects, whose importance has come to be increasingly appreciated in the last few years.

After a somewhat short introduction—there is no general historical synopsis—the second chapter treats in detail the conformation, formation and hydrolysis of *O, N,* and *S* acetals. Here the author—and the reviewer—prefers the explanation involving the concept of anomeric effect and *exo*-anomeric effect as stabilizing delocalization of nonbonding electron pairs in σ^* orbitals rather than the alternative interpretation as the destabilizing interaction of nonbonding electron pairs (rabbit ear effect). The oxidation of the acetal C–H bond makes the transition to the next two main chapters, which treat the conformation, formation and hydrolysis of esters, amides and similar compounds. The author adeptly presents his theory concerning the formation and decomposition of tetrahedral ortho ester structures and comments on the results obtained by his and other groups since the famous report in Tetrahedron (1975).

The next three chapters are dedicated to stereoelectronic effects in reactions at saturated and sp^2- and sp-unsaturated systems. The reactions discussed include the S_N2 and S_N2' reactions, the rearrangements of secondary and tertiary alcohols with vicinal leaving groups, the Wagner-Meerwein rearrangement, the nucleophilic addition at carbonyl and iminium compounds and α,β-unsaturated ketones, the reduction of α,β-unsaturated carbonyl compounds, E2 and E1cB reactions, the Grob fragmentation, the addition of electrophiles to enolates and the addition of nucleophiles to triple bonds. The next chapter, entitled "Potpourri", discusses further rearrangements, including the reaction of ortho esters with Grignard reagents, the intramolecular aldol reaction, the ring opening of β-lactams, and the dipolar cycloaddition of glycosylnitrones. A new synthesis by the author's group of erythronolide A is also included. In this an intermediate 1,7-dioxaspiro[5.5]undecane was synthesized by the exploitation of stereoelectronic effects. The last chapter deals with such effects in enzymic reactions. The book is rounded off by comprehensive author and subject indexes.

This monograph is distinguished by its clear organization, precise language and cleanly designed formula diagrams. The author has succeeded in extracting the essential stereoelectronic aspects from the voluminous literature and in discussing them pertinently. He presents the work of his own group just as clearly and develops his theories therefrom in a factual manner which is easily understood. The wide range of reactions treated and the plethora of references at the end of every chapter (over 700 references in all) make this book an important work of reference for every chemist or student with an interest in organic chemistry.

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Pyrolysis: Theory and Industrial Practice. Edited by *L. F. Albright, B. L. Crynes,* and *W. H. Corcoran*. Academic Press, New York 1983, xviii, 482 pp., bound, $ 65.00.

In 18 chapters several authors principally deal with the manufacture of ethylene and other olefins, diolefins and aromatics from various feeds. The carbonization of solid fuels such as coal, oil shale and biomass for the production of liquid products, the widely utilized coke oven technology, and the pyrolysis of plastic wastes are only treated briefly. The coking of heavy oils and tar sands, which also belongs to the broad area of pyrolysis is not considered.

The theoretical treatise in the initial chapters is mainly concerned with the reaction mechanisms of cracking methane through butane and other paraffins and olefins, diolefins, naphthenes and aromatics. Practice leads theory in cracking mixtures; data on the production of light cracking products from feeds not originating from crude oil such as coal, tar, shale oil, polyolefins, and biomass are mainly empirical in nature.

A further theoretical chapter deals with the mathematical modelling of the reactor and the pyrolysis reactions of hydrocarbon gases, naphtha and gas oils. Sensibly defined peripheral conditions yield reliable predictions with an acceptable amount of effort.

Coke formation and gasification are of considerable importance in running industrial pyrolysis plants. The treatment of these complex problems reveals the limits of knowledge in this area. A separate chapter is devoted to undesirable reactions on the metal surfaces of reactors such as carbonization, coke formation, and the decomposition of ethylene. Measures for prevention and control are presented.

The discussion of the theory and application of laboratory reactors to investigate the kinetics of pyrolytic reactions covers the most important types of reactors.

The rest of the book is aimed at those readers who are mainly interested in the technology and operation of pyrolysis plants for the production of base products for the petrochemical industry. The topics not only include cracking in tube furnaces as normally used nowadays, together with the preparation of the feedstock, but also other technologies such as cracking with gaseous or solid heat transport media or in the presence of catalysts. The cracking reactors discussed include not only the normal tube furnace but also alternatives such as molten bath, entrained bed or fluidized bed reactors; the economic aspects of the technologies are also discussed. Furthermore, the economic questions concerning olefin production are discussed both retrospectively and with an eye to the future.

Descriptions of material problems in tube furnace construction, process monitoring and quench coolers for the recovery of heat from the furnace effluent gases complete a book primarily intended for engineers and chemists concerned with the building and operation of pyrolysis plants.

Bibliographies for every chapter permit more intensive study. When American units are quoted, they are usually accompanied by their SI equivalents. In spite of the fact that the book is focussed on the question of producing low molecular weight olefins, it is also useful for understanding other thermal processes.

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Chemie der Räucherung. By *L. Toth*. A publication of the Deutsche Forschungsgemeinschaft. Verlag Chemie, Weinheim 1982. xi, 331 pp., stitched, DM 68.00.

This monograph provides a comprehensive 100-page literature survey of the smoking of foods (smoke production, manufacture of smoke condensates, composition of the curing smoke, the effects of smoking). Then follows a discussion by the author of the investigations of the phenol fraction of curing smoke (ca. 140 p.) that he carried out at the Bundesanstalt für Fleischforschung at Kulmbach (production and condensation of curing smoke, analysis of the phenol extracts, the influence of the smoking technique on the composition of the phenol fraction, phenols in smoke essences and smoke flavors, phenols in smoked meat products).

Then follows an experimental portion (ca. 25 p.), a list of all the smoke components so far described, classified according to compound type (306 compounds on ca. 50 p.) and a bibliography (147 references).

This book is an excellent source of information for every type of chemical and technological question concerning the smoking of food and hence a solid basis for toxicological discussions. It belongs in every relevant library.

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Computeranwendungen in der Chemie. By *K. Ebert* and *H. Ederer*. Verlag Chemie, Weinheim 1983. ix, 359 pp., bound, DM 63.00.

Almost every scientifically definable field requires the participation of another on many occasions. Classically these are spoken of as auxiliary sciences, a phrase that sounds somewhat condescending and is often meant to be so. If a scientist combines this auxiliary science intensively with his original field, he is often treated as an outsider and may become an object of amusement. However, it can happen that what was once an auxiliary science penetrates large portions of the original and transforms it. Amongst the natural sciences one only needs to mention the thrust of mathematics into physics, and chemistry into biology. Recently mathematics, information science, and computer science have been extending their role within chemistry. Theoretical chemistry without mathematics and high performance instrumental analysis (FT-IR, GC-MS, FT-NMR etc.) without data processing are unthinkable. But techniques of instrumental analysis that are now regarded as being classical (IR, UV, GC etc.) have also been conquered by information science and data processing since the application of microprocessors. Nevertheless, the university education of German chemists takes but slight account of these trends. This gap has to be filled at the moment by the further education program of the GDCh (German Chemical Society).

This present book is aimed at filling just this gap. The hurdle of learning a high level programming language (in this case BASIC) is skillfully bypassed. Using simple chemically oriented examples a didactically very clever introduction is presented to the programming of personal computers. The exemplary programs are concisely and clearly constructed: commentary, input, calculation and output. They are written using the minimum of BASIC which is available with the cheapest personal computer. However, in certain cases reference to more capable computers would have been sensible; even though they seem costly, programming time would have been saved.

The severity of both the problems treated and the programming technique has been chosen in a didactically very refined manner. Numerical integration, equations, linear systems, differential equations, and nonlinear systems are treated. In some cases a somewhat more critical presentation of the mathematics would have been desirable. Examples are numerical problems in matrix inversion or the problem of the linearization of measured data (it is treated using the Arrhenius equation). In other cases (e.g. Fourier series) a more detailed presentation of the problem would have been very useful in the book.

This book can be recommended to every chemistry student as a textbook and a book to work through, as an introduction to personal computers. The simple utilization of the programs is not to be recommended since it is without didactic worth. It would be even more senseless, for those who wish to learn, to purchase the programs ready for use as diskettes or tapes. The undeniable virtue of this book lies in the fact that it offers the possibility of familiarizing oneself independently with the fascinating world of small computers.

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Organic Synthesis. Concepts, Methods, Starting Materials. By *J. Fuhrhop* and *G. Penzlin*. Verlag Chemie, Weinheim 1983. xi, 355 pp., bound, DM 78.00.

With the increasing importance of chemical synthesis, the problems of synthesis planning and execution have become focuses of interest. The number of recently published books, dealing with the strategy and techniques of synthesis, mirror this development. This book is intended to provide advanced students and research chemists with knowledge of educts, target molecules and the concepts and methods concerning their transformation.

The first chapter deals with the construction of carbon chains and carbocycles, whereby the authors apply Corey's synthon concept including the idea of "Umpolung" as a useful heuristic principle. Here, as in many other publications, there is no strict differentiation between a synthon as originally formulated by *Corey* and the reagents corresponding to this concept. It is inevitable that this point of view—analysis of the target compound into synthons—should lead to the neglect of one of the most important aspects of organic chemistry, namely stereochemistry.

The steric course of the reaction is then discussed using individual examples. Some methods of carbon-carbon bond formation, e.g. the Wittig reaction, are thoroughly discussed mechanistically, at the same time drawing stereochemical conclusions. Just as thorough a discussion of the aldol reaction would have been desirable, since, in its many newly developed variations, it vividly demonstrates the powerful nature of organic chemical synthesis.

The pattern is similar in the next chapter which deals with the transformation of functional groups. The Sharpless epoxidation for the stereoselective synthesis of polyhydroxy compounds is amongst the omissions here; no account is taken of recent highly selective reducing agents or microbiological reductions; some important protecting

groups remain unmentioned although a special section is devoted to them.

The third section returns to the subject of the first and retrosynthetic analysis is undertaken of simple organic compounds by use of the synthon concept. A comprehensive list of commercially available fine chemicals, which is contained in the chapter, indicates to the reader how far back the retrosynthesis must be taken.

The fourth chapter constitutes nearly half of the whole work and presents the synthesis of particular compound classes. Instead of developing the retrosynthetic discussion, begun in Chapter 3, at the level of more complex molecules an enormous range of synthetic examples has been assembled and once again stereochemical problems are only treated superficially.

In the chapter on steroids, the toys with which stereoselective syntheses were developed, a chance has been lost of emphasizing the synthesis of pure enantiomers, in particular by the application of asymmetry-inducing synthetic steps. The choice of other synthetic examples would have easily made this possible. For the vitamin B_{12} syntheses, which are attached to a section dealing with porphyrins, chlorophyll a and corrins, the authors ought to have been able to include examples concerning the strategies for the solution of stereochemical problems alongside those dealing with the construction of the skeleton. The syntheses of vitamin B_{12} are copybook examples in this respect. The macrolide syntheses are another example that could be cited, of which only one is mentioned. Here it would have been possible to illustrate various synthesis strategies by means of other examples. Since the macrolides were the test bed for the development of stereoselective aldol reactions, this offered the possibility of renewed discussion of the theme, which was introduced in the first chapter, at a more advanced level.

The reader is confronted by a superfluity of examples without the interrelationships being revealed. The authors would have been well advised to discuss fewer examples in terms of the synthon concept and to bring out the important stereochemical aspect by adept choice of the right examples of syntheses.

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The Handbook of Environmental Chemistry. Edited by *O. Hutzinger*. Vol. 3, Part C: Anthropogenic Compounds. Springer-Verlag, Heidelberg 1984. xiv, 220 pp., bound, DM 138.00.—ISBN 3-540-13019-5

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Corrigendum

The following correction should be made to the review article entitled "Chelation or Non-Chelation Control in Addition Reactions of Chiral α- and β-Alkoxy Carbonyl Compounds" [New Synthetic Methods (44)] by M.T. Reetz, *Angew. Chem. Int. Ed. Engl. 23* (1984) 556:

In the last column of Table 1 on p. 561 the *syn*:*anti* ratios for the simple diastereoselectivity should read (from top to bottom) 77:23, 80:20, 65:35, 66:34, 63:37, 64:36, 66:34, and not as printed.

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Gas Chromatographic Separation of Enantiomers on Optically Active Metal-Complex-Free Stationary Phases**

New Analytical Methods (24)

By Volker Schurig*

If a stationary phase A employed in gas chromatography possesses a chemical affinity for substance B, which is to be separated, then the retention behavior is not only determined by the normal *physical* equilibrium between the gas and liquid phases but also by the *chemical* equilibrium $A + B \rightleftharpoons AB$. If A and B are chiral and A is present in optically active form while B is a racemic mixture, then it is possible to achieve a gas chromatographic enantiomer resolution without the isolation of diastereomers: the energetically different diastereomeric associates $A_R B_R$ and $A_R B_S$ are formed rapidly and reversibly. This enantiospecific resolution principle was first demonstrated in 1966 by the quantitative resolution of racemic amino acid derivatives on optically active peptide phases in analogy to the well-known stereospecificity of enzymes. The anchoring of the chiral resolving agent to thermally stable polysiloxanes together with the employment of high resolution capillary columns and the use of appropriate derivatization strategies has led to the development of enantiomer resolution into a routine modern method for many classes of substances. The demonstration of enantiospecificity in the gas chromatographic separation process is of fundamental interest, and its systematic study can result in a significant contribution to the understanding of the molecular mechanism of "chiral recognition". The gas chromatographic separation of enantiomers has also proven to be an accurate and sensitive method for the determination of the enantiomeric composition of natural products and products of enantioselective transformations (asymmetric syntheses, "chiral pool" transformations, kinetic resolutions, biomimetic reactions) and for the quantification of racemization, e.g. in the synthesis and hydrolysis of peptides. In any research program devoted to the phenomenon of chirality, the gas chromatographic separation of the enantiomers of volatile compounds constitutes an indispensable modern instrumental technique.

1. Introduction

The phenomenon of optical activity is one of the most fascinating manifestations of living matter which has inspired the chemist to many imitations in the laboratory ever since the founding of stereochemistry. The resolution of synthetic racemic mixtures by methods analogous to those of *Pasteur* in his pioneering investigations is of undiminished importance both as a preparative method for the isolation of pure enantiomers and as an analytical tool for the determination of enantiomeric compositions. The availability of high-performance methods of enantiomer analysis has become urgently necessary in order to keep

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[**] The separation of enantiomers on optically active metal-complex stationary phases ("complexation gas chromatography") will not be discussed here.

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pace with the development of highly enantioselective reactions[1] (asymmetric synthesis, kinetic resolution, "chiral pool" syntheses, enzymatic transformations) and to cope with the requirements of mechanistic investigations.

Enantiomer resolution by gas chromatography constitutes a technique that allows the exact determination of enantiomer composition, the determination of enantiomer purity up to 99.9%, and the assignment of absolute configurations employing subnanogram quantities for many groups of compounds[2]. Furthermore, the method is suitable for the investigation of the phenomenon of chiral recognition and can in this way contribute to an understanding of structure/activity relationships and the enantiospecific interaction of chiral selectors and selectands[3a].

The resolution of enantiomeric mixtures by gas chromatography can be performed in two **modes**[4]:

a) *Indirect method:* conversion of the enantiomers into diastereomeric derivatives by chemical reaction with an auxiliary, enantiomerically pure, chiral resolving agent and subsequent gas chromatographic separation of the resulting diastereomers on an achiral stationary phase.
b) *Direct method:* Gas chromatographic separation of the enantiomers on a *chiral* stationary phase containing an auxiliary resolving agent of high (but not necessarily complete) enantiomeric purity.

An alternative method, when the chiral agent is mixed with the mobile gas phase, has also been described[5a].

These processes rest on the use of a chiral non-racemic auxiliary agent and hence constitute variants of the classical method of enantiomer resolution via diastereomeric salts according to *Pasteur*. Chromatographic resolution of enantiomers *without* the employment of a chiral auxiliary agent is, in analogy to the construction of a perpetual motion machine, impossible according to the present state of scientific knowledge. Reports of enantiomer resolution in achiral systems seem either unreliable[5b, 5c], require a rigorous examination[5d], or they do in fact involve a chiral agent, e.g. as internal standard[6].

While method (a) involves the formation and isolation of *diastereomers* before separation, method (b) involves the rapid and reversible *diastereomeric interaction* between optically active selector and racemic selectands. A prerequisite for method (a) is the presence of a reactive chemical function in the enantiomers which allows quantitative reaction with an optical active reagent. Racemization of the sample on derivatization or kinetic resolution at incomplete conversion obscures the original enantiomer ratio. The diastereomeric ratio to be determined can also be altered by accidental fractionation during derivatization, work-up and chromatographic analysis (injection, detection). Systematic errors always occur if the chiral agent is not present in complete enantiomeric purity or is racemized during the derivatization reaction. Such sources of error can be detected by a combination of methods (a) and (b), i.e. by employing a chiral phase which resolves all four configurational isomers.

The direct resolution of enantiomers by method (b) is of necessity more difficult in that, apart from the chiroptical parameters, all physical and chemical properties of optical antipodes are identical in an achiral environment. If the gas chromatographic retention volume V' of the selectand is expressed as a product of the vapor pressure p^0 and the activity coefficient γ

$$V' = p^0 \cdot \gamma$$

then the resolution of enantiomers (R and S), which is expressed in terms of the separation factor α,

$$\alpha = p^0_R \cdot \gamma_R / p^0_S \cdot \gamma_S$$

can only take place as a result of a difference in the vapor pressure *or* the activity coefficient[7]. While the presence of an optically active component in the mobile phase would appear to alter the vapor pressures p_R and p_S, the employment of a chiral stationary phase can lead to a discrimination of γ_R and γ_R because of the differing stabilities of the diastereomeric associates of selector and selectand.

Method (b) is characterized by the introduction of chemical selectivity into the gas chromatographic separation process, whereby chiral recognition is caused by the molecular association between the racemic selectand and the optically active selector in the stationary phase.

An optically active stationary phase is of itself no guarantee for an effective enantiomer resolution. On using a high resolution capillary column, a quantitative resolution is achieved only when the difference between the free enthalpy of diastereomeric association for the enantiomers is at least 10 cal/mol (22 °C). The success of enantiomer resolution should always be verified by control experiments. Peak coalescence, when a racemic phase is used, and peak inversion of nonracemic mixtures on employment of chiral phases of the opposite configuration are unequivocal criteria of enantiomer resolution[8].

This progress report will only be concerned with the direct method (b) of gas chromatographic enantiomer resolution. At present two well-developed methods are available which are complementary to each other:

- *Resolution of enantiomers on optically active amino acid and peptide selectors via hydrogen bonding*[4, 9, 10].
- *Resolution of underivatized enantiomers on optically active metal chelates by coordination interaction ("complexation gas chromatography")*[11].

The first reproducible and quantitative gas chromatographic enantiomer resolution was achieved in 1966 by *Gil-Av, Feibush* and *Charles-Sigler* at the Weizmann Institute of Science[12]. *Gil-Av* had previously investigated the resolution of racemic amino acids by the indirect method[13] and now sought to employ the chiral agent not for derivatization but as an additive to the stationary phase. The contemporary state of the art of gas chromatographic enantiomer resolution should not blind us to the initial difficulties with which the method was beset: "with a state of frustration"[4]. In retrospect *Gil-Av* may be **quoted**[14]:

"A considerable number of workers all over the world have tried to solve the problem of the resolution of antipodes by this method (i.e. gas chromatographically) without any success. When we turned to this research topic al-

most all the workers in the field had given up the idea as impracticable. And not only that: because many reports of positive results had proved to be in error, the topic had fallen into disrepute".

"After long and painstaking effort, which was accompanied by many a disappointment, we finally discovered a solution to the problem. The core of the matter was to find a liquid for wetting the walls, that in some respects imitated an enzyme. ... To our surprise it turned out that amino acids ... retained to a certain extent the ability of the larger enzyme structures to distinguish between left- and right-handed molecules ... (cf. Fig. 1). We were thus able to add an important new method for the study of optically active molecules to those developed by *Pasteur* and other workers."

The demonstration of enantiospecificity in a gas chromatographic system as a counterpart to the already known liquid chromatographic racemate resolution[15-17] was of itself remarkable, particularly since the resolution occurred quantitatively (cf. Fig. 1). Furthermore, the manifold possibilities for its application, which result from the advantages of the gas chromatographic method (high performance, sensitivity, reproducibility, precision, simple detection), were realized immediately. The ability to resolve minute quantities of amino acid enantiomers coincided with the intensive efforts to demonstrate the presence of biogenic materials in interstellar space, in meteorites and in lunar samples from the NASA Apollo moon program. The cooperation of *Gil-Av* with biophysicists and peptide chemists at the University of Houston, Texas, *E. Bayer, J. Oró, W. Parr,* and *W. A. Koenig,* produced important advances which, with the employment of thermally stable chiral polysiloxane phases, laid the foundations for the rapid development of gas chromatographic enantiomer resolution as a routine, modern, high-performance method[9, 10].

In 1969 *Gil-Av* and *Schurig* attempted to extend the area of application of method (b) for gas chromatographic enantiomer resolution to other classes of compounds. Chiral unsaturated hydrocarbons, ethers, esters, ketones etc. are not resolvable or only resolvable with difficulty into their enantiomers via formation of diastereomeric salts. Thus the enantiospecific coordination interaction of racemic selectands with optically active organometallic selectors was regarded as an important complementary possibility for gas chromatographic chiral recognition because of the variety and variability of metal complex structures and of optically active ligands.

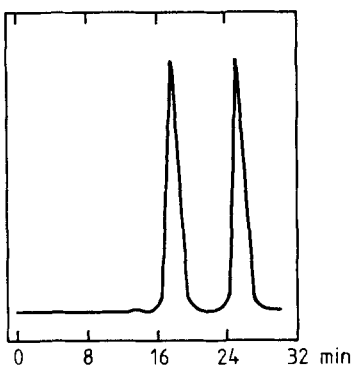


Fig. 1. Gas chromatographic resolution of a racemic amino acid mixture according to *Gil-Av* [14].

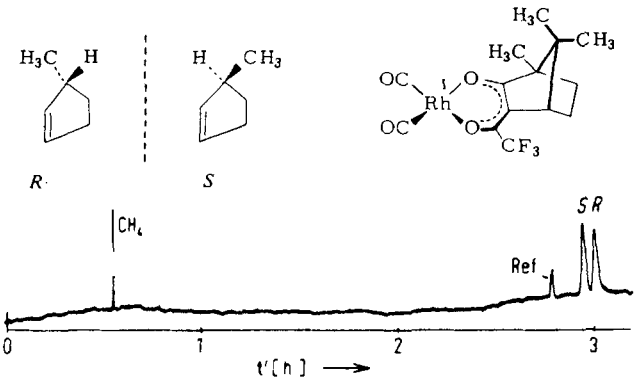


Fig. 2. Gas chromatographic resolution of racemic 3-methylcyclopentene on an optically active metal chelate by enantiospecific coordination interaction [8].

By analogy with the resolution of racemic *trans*-cyclooctene via crystallization of a diastereomeric platinum-π-complex by *Cope* et al.[18], it was decided to test whether a racemic olefin could be resolved gas chromatographically into its enantiomers without the isolation of diastereomers, on the basis of the diastereomeric interaction of the enantiomers with a chiral metal complex. This principle, whose practical realizability has at one time been doubted[19], was first realized in 1977, as a result of improvements in gas chromatographic instrumentation, with demonstration of the resolution of racemic 3-methylcyclopentene on dicarbonylrhodium-3-trifluoroacetyl 1*R*-camphorate[8], a selector-selectand system that was first conceived in 1971[20,21] (cf. Fig. 2):

Although this successful experiment demonstrated that gas chromatography possesses the necessary thermodynamic and kinetic prerequisites for chiral recognition by coordination interaction, this resolution principle has not yet been generalized for olefins. The method, however, was extended to oxygen, nitrogen, and sulfur-containing compounds by the employment of chiral bivalent transition metal bischelates and led to a rapid extension of complexation gas chromatography for the resolution of enantiomers[11,22] (see footnote [**] on p. 747).

The methods available today for the quantitative gas chromatographic resolution of enantiomers offer many possibilities for their application and investigation. It is appropriate here to differentiate between the information which is accessible from the various peak parameters[22] (Table I).

Table 1. Gas chromatographic parameters in enantiomer resolution.

Peak parameter	Definition
Peak retention	A thermodynamic measure of the selective interaction between the selector and the selectand (K, $-\Delta G°$)
Peak separation	A thermodynamic measure of the enantiomer discrimination between the enantiomerically pure selector and the racemic selectand ("chiral recognition") ($-\Delta_{R,S}(\Delta G°)$)
Peak ratio	A quantitative measure of the enantiomeric composition of the selectand ('enantiomeric excess' (*e.e.*) [2])
Peak assignment	Assignment of the absolute configuration of the selectand by correlation of the order of elution and the molecular configuration
Peak coalescence (second kind)	A kinetic measure of the enantiomerization of the selectand during resolution (ΔG^{+})

The *peak retention* of the selectand is determined by the (physical) partition equilibrium between the gas and liquid phases *and* by the (chemical) association equilibrium which arises when the selector exhibits chemical affinity towards the selectand. In the case of complexation gas chromatography the equilibrium constant for association K and, for variable temperature studies, the Gibbs-Helmholtz parameters ΔH° and ΔS° are easily accessible from relative retention data[23].

The *peak separation* of racemic selectands on chiral selectors is exclusively the result of the differences between the free enthalpies of association, $-\Delta_{R,S}(\Delta G^\circ)$. Although there should be no doubt that there will always be a difference in the free enthalpies of association for each chiral combination of selector and selectand, practical results are only anticipated with the employment of optimized systems that exhibit effective chiral recognition. Gas chromatography is an effective method of acquiring thermodynamic data of enantiomeric discrimination. In this respect, the question of the proportionality of ΔG° and $\Delta_{R,S}(\Delta G^\circ)$ is of interest. The intuitive assumption that an effective enantiomer discrimination is only to be expected via a strong chemical interactions turns out to be false and has been disproved in many instances. The impeding of molecular association, e.g. by steric effects, seems indeed to be advantageous for the discrimination of configurational isomers. Analogously to enzyme models, enantiomeric discrimination in chromatographic systems has been interpreted by *Dalgliesh* in terms of "three point interaction" between selector and selectand ("three point rule")[24]. The three point theory requires three effective bonds between selector and selectand for a favorable interaction. Later on, this model had to be altered so as to require a minimum of three stereochemically important interactions for enantiomer differentiation[7]. Along with bonding interactions (hydrogen bonds, charge transfer interactions, coordination) these can also include nonbonding interactions (steric hindrance). Thus, in principle, it ought to be possible to resolve a nonfunctionalized racemic alkane by host-guest interaction with a chiral clathrate forming compound by physical inclusion. The recently observed gas chromatographic resolution of racemic pinenes on an α-cyclodextrin inclusion compound points in this interesting direction[25].

In contrast to enzymes, chiral catalysts, and chiral NMR shift reagents, it is only possible for chromatography to distinguish between enantiomers ("enantiomorphy"), but not between enantiotopic groups or faces ("enantiotopy"). For this reason enantiospecific selector/selectand systems are only suitable model systems for the specificity of enzymes with respect to enantiomers or of receptors with respect to the enantiomers of pharmaceuticals, pheromones, odorants etc. A comparison of enantiospecificity is then only possible in a thermodynamic sense. The realm of enzymatic reactions, i.e. the reaction of prochiral educts to yield chiral products, has no analogue in a gas chromatographic experiment, since the prochiral substrate cannot be discriminated nor can a chemical reaction occur which leads to a chiral product.

The *ratio* of the peak areas is a direct measure of the ratio of the amounts of the enantiomers. The measured enantiomer ratio corresponds to the actual enantiomer ratio of the sample when all the chemical, physical and analytical manipulations, including injection and detection, are carried out in an achiral environment. A falsification of the enantiomer ratio, if any, would only be possible as a consequence of an enantioselective decomposition or an irreversible adsorption of the sample by the optically active stationary phase during chromatographic elution. The advantages of the gas chromatographic determination over other methods for the determination of the enantiomeric purity *e.e.* (enantiomeric excess)]

$$e.e. = \frac{R-S}{R+S} \times 100\%$$

have recently been discussed in detail by *Schurig*[2]. Typical advantages are sensitivity of detection, high accuracy, and reproducibility. The method is also independent of the chiroptical properties of the sample (e.g., the magnitude of the specific rotation) and optically active impurities do not interfere. Gas chromatography is particularly suitable for two limiting cases: for the detection of small enantiomeric excesses (e.g. during the investigation of the accumulation of optical activity in the laboratory under abiotic conditions) and for the proof of very high enantiomeric purity (e.g., for the determination of traces of enantiomers during investigations of the enantiospecificity of enzymes, during kinetic resolution experiments and enantioselective synthesis). When the separation factor is high, gas chromatography can even detect 0.1% of an enantiomer. Such a contamination corresponds, for an enantioselective reaction from a prochiral precursor (*e.e.* = 99.8%), to a difference in free enthalpy of the diastereomeric transition state of "only" $\Delta\Delta G^{\neq} = 4$ kcal/mol at 18 °C[2].

The derivatization-free resolution of enantiomers by complexation gas chromatography is particularly suitable for analytical applications, since this method allows the determination of the enantiomeric composition directly in the vapor phase without the necessity for substrate isolation. Thus, the course of an asymmetric reaction can be followed by repeated determinations without interrupting it, and, for example, alterations of enantioselectivity by autocatalysis or kinetic resolution of the product can be easily recognized[26].

The *peak assignment* requires a knowledge of the molecular configuration of the selectand. Since gas chromatographic enantiomer resolution depends on the enantiospecific association between selector and selectand, it ought to be possible to formulate rules for substrates that belong to homologous series, which correlate the retention time with the absolute configuration[27,28]. The absolute configuration can, if necessary, be determined with only 10^{-9} g of substance e.g. for an enzymatic reaction by the co-injection of a reference compound of known chirality. In the case of an *enantiomerically pure* sample or reference substance, an aliquot of the other enantiomer (or of the racemate) must be coinjected for purposes of peak identification. The determination of the configuration of the selectand by gas chromatography is independent of the chiroptical properties of the selector, which, in principle, is not required to be either enantiomerically pure or of known configuration.

A *peak coalescence (of the first kind)* is observed, as mentioned, if a racemic mixture is employed instead of the optically active selector. It is possible in this way to distinguish achiral diastereomers and other isomers from enantiomers, since only enantiomers coalesce. A *peak coalescence (of the second kind)* occurs during the chromatographic resolution when configurationally labile enantiomers invert. "Enantiomerization" of the selectand leads to an interconversion peak profile, from which kinetic parameters of inversion, as a reversible first order reaction, can be calculated[22,29]. Whereas at slow inversion a plateau, which is produced by the inverting molecules, appears between the terminal peaks, a rapid configurational interconversion destroys resolution.

Because of its high resolving power gas chromatography is particularly suitable for enantiomer analysis, while for liquid-chromatographic enantiomer resolution the emphasis is on the preparative aspect[30–32]. However, when the separation factor is large, $\alpha > 1.3$, gas chromatography may also be employed for the preparative resolution of enantiomers in the mg to g sample range. The isolation of pure enantiomers is suitable for chiroptical investigations, for biological tests or, in the case of chiral radiochemicals, for labeling experiments. In principle, it is possible to obtain 100% enantiomerically pure enantiomers even though the selector may not be enantiomerically pure.

Gas chromatographic methods of enantiomer resolution (see footnote [**] on page 747) and their applications and mechanisms will be discussed in the following section.

2. Gas Chromatographic Enantiomer Resolution via Hydrogen Bonding

2.1. Pioneering Investigations

The first claims of the resolution of racemic substrates (2-butanol, 2-bromobutane) on optically active stationary phases (starch, diethyl tartrate/Al_2O_3) were made by *Karagounis* and *Lippold*[33]. Other authors were unable to repeat the resolutions, which were only marginal anyway[34,35] or were caused, in the case of 2-bromobutane, by dehydrohalogenation to *E*- and *Z*-2-butene (1 : 1) in the injection port[36]. In spite of considerable instrumental shortcomings, later investigations by *Karagounis* and *Lemperle*[37] pointed the way to interesting future developments, e.g. preparative racemate resolution using polarimetry as an enantiospecific detection system or the use of chiral metal coordination compounds (Δ-$(Co(en)_3)Br_3/Al_2O_3$) as an enantiospecific stationary phase. An "inverse" system, namely the gas chromatographic resolution of volatile, racemic chromium(III) *tris*-hexafluoroacetylacetonate on pulverized *d*-quartz was also investigated[38]. It has since proved impossible to establish with certainty whether or not a marginal degree of enantiomer resolution was achieved in these experiments. Attempts to resolve racemic alcohols (2-alkanols, 3-menthanols) on various optically active stationary phases ((+)-2-octyl sebacate, (+)-dimethyl tartrate, peracetylated sucrose) were without success[35,39].

It was only with the introduction of high performance capillary columns for gas chromatography and the development of high sensitivity detection systems that the conditions were met which led to the development of tailored selector/selectand systems and their optimization to high resolution performance. Mainly those enantiospecific resolution systems that yield *quantitative* (baseline) resolutions of racemic mixtures under the instrumental conditions employed will be reviewed in the following discussion.

2.2. The Resolution of Derivatized Selectands on Optically Active Amino Acid and Peptide Selectors via Enantiospecific Hydrogen Bonding

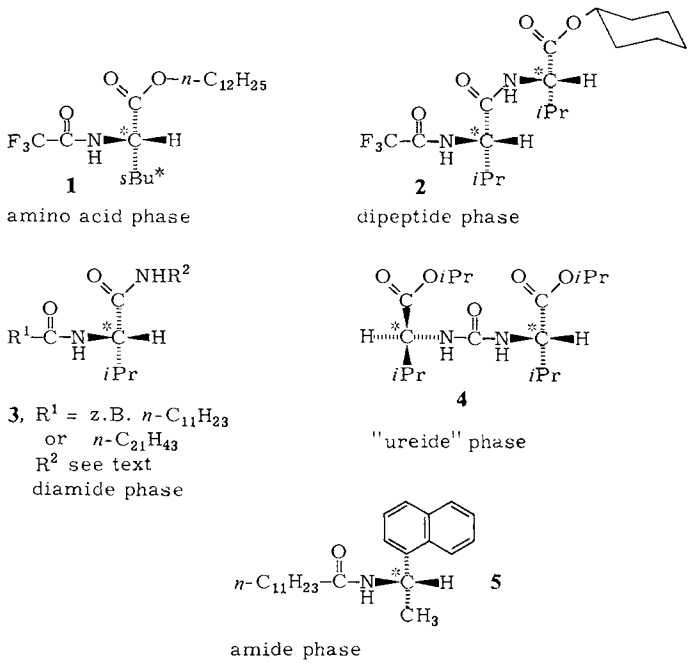
In 1966 *Gil-Av, Feibush,* and *Charles-Sigler* described the first reproducible resolution of 18 racemic, protein amino acids as their *N*-trifluoroacetyl(TFA) alkyl esters in glass capillaries coated with optically active *N*-TFA-L-isoleucine dodecyl ester **1** or *N*-TFA-phenylalanine cyclohexyl ester[12,40]. The design of this enantiospecific selector/selectand system was based on the idea of biomimetically imitating the stereospecific peptide enzyme interaction employing simple amino acid entities as model substances. In order to achieve this it was thought necessary to employ a high-performance capillary column to amplify the minute chiral recognition effect. This fundamental discovery by *Gil-Av* et al. was the starting point of a fruitful development, particularly by the research groups of *Gil-Av, Bayer,* and *König,* from a supposed curiosity with rather archaic-looking chromatograms[12] into a highly developed routine method for the resolution of the enantiomers of many important classes of compounds by gas chromatography[4,9,10]. This development was inspired by the multiplicity of possible applications on the one hand and by the interest in the mechanism of chiral recognition—as a model for the enantiospecific enzyme substrate interaction—on the other.

Gil-Av et al. ascribed the resolution to the rapid reversible molecular association of the enantiomers with the asymmetric molecules of the optically active stationary phase[12,40]. In order to increase the various steric and polar interactions between the diastereomeric associates, both the derivatization strategy for the amino acids to be resolved and the structure of the stationary phase were varied systematically. The results have been summarized in two detailed review articles[41,42].

Scheme 1 includes the structures of the most important optically active stationary phases for the enantiomeric resolution of amino acid derivatives and other nitrogen-containing racemates via hydrogen bonding.

The "second generation" phases **2**—**4** introduced by *Gil-Av* and *Feibush* exhibit better enantiospecificity than the amino acid phase **1** because of the presence of an additional amido function capable of hydrogen bonding[43–50] The first dipeptide phase tested, *N*-TFA-L-valyl-L-valine cyclohexyl ester **2**, already proved capable of the preparative resolution of racemic *N*-TFA-alanine *tert*-butyl ester on a packed 2-m column[51]. The arsenal of dipeptide phases[42] has been greatly enlarged by many investigations[52–66].

A systematic investigation has been made of the influence of the *N* and *C*-terminal amino acids of *N*-TFA-*O*-cyclohexyl derivatives of the dipeptides Val-Val[67] and

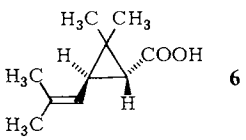


Scheme 1. Representative structures of optically active amino acid and amide stationary phases for the resolution of enantiomers via hydrogen bonding.

Phe-Leu[67,68] on the order of elution of *N*-TFA-amino acids. An expected peak inversion was observed with the mirror image phases L-Val-L-Val and D-Val-D-Val. On diastereomeric phases, e.g. L-Val-L-Val as compared to D-Val-L-Val or L-Val-D-Val, peak inversion only occurred on changing the configuration of the *N*-terminal amino acid. Hence the enantiospecificity of dipeptide phases is largely governed by the *N*-terminal amino acid. This was also confirmed by the finding that the dipeptide phase Gly-L-Val possesses significantly inferior separating properties than L-Val-Gly[67]. Accordingly the employment of tripeptide phases, e.g., *N*-TFA-L-valyl-L-valyl-L-valine isopropyl ester did not bring about any improvement in the separation factor but merely decreased the volatility as compared to dipeptide phases[44,68]. The diamide phases **3** developed by *Gil-Av* and *Feibush*[48-50,70-73] are derived from the peptide phases **2** by the removal of the *C*-terminal amino acid, which does not invoke any significant contribution to enantiomer discrimination. Phases of type **3** contain two thermally stable amide functions capable of hydrogen bonding, but only one asymmetric center, and are more enantiospecific than type **2** phases. A systematic investigation has been made of the influence of the alkyl residues R^1 and R^2 of the valine diamide phase **3** on the separation factors of *N*-TFA-α-amino acid alkyl esters[50]. The alkyl residues R^1 and R^2 influence the resolution because of their steric requirement, whereby R^2 plays a dominating role. It was found to be advantageous if R^1 constitutes the long chain residue necessary for thermal stability (n-$C_{11}H_{23}$). A decrease in the resolution in the order *tert*-butyl > cyclooctyl > neopentyl was observed for R^2. The thermally stable (up to 190°C) and less volatile phases **3**, R^2 = 1,1-dimethylhexadecyl[72] are very promising resolution phases for racemic amino acid derivatives; one phase is commercially available[71]. The high separation factors also permit preparative resolutions on packed columns[69,70]. Racemic β- and γ-amino acid derivatives[74] and derivatized 1,2- and 2,1-amino alkanols can also be separated on diamide phases **3**. Further applications of diamide phases **3** concern a diamide-diamide selector/selectand system, i.e. the resolution of racemic *N*-TFA-amino acid *tert*-butylamides on the *N*-lauroyl-*tert*-butylamides of optically active α-amino acids[75]. α-Methyl-α-amino acid amides and α-halogenocarboxylic acid amides have also been resolved on diamide phases **3**[76,77]. A concise summary of the synthesis and application of diamide phases in gas chromatographic enantiomer resolution is available[78a].

The *N,N'*-carbonyl-bis(amino acid ester) phase **4** (incorrectly named "ureide" phase in the original literature) is particularly suitable for the resolution of racemic *N*-TFA-substituted amines $RR'HC-NH_2$[43]. These phases contain two structurally equivalent NH- and CO-functions capable of hydrogen bonding in close proximity to the asymmetric center. The influence of the consistency of the "ureide" phases (liquid, liquid crystalline, solid) on the separation factor has been investigated in great detail[79-82]. Stationary phases in the solid state exhibited large separation factors α, but also a considerable amount of peak broadening, particularly for the amino acid enantiomers that were eluted as the second peak[79]. In spite of the anomalous peak shapes, the high separation factors α that could be achieved with the mesophases permitted quantitative resolutions on short packed columns[81]. *N,N'*-Carbonyl-bis(L-valine isopropyl ester) **4** and the D-leucine analogue have been employed in the smectic mesophase for the resolution of the racemic amines (*N*-perfluoroacylated 1-phenylethylamines)[82]. The close temperature range lying 10—20° below 100°C seems disadvantageous.

It was demonstrated by means of phase **5** (*N*-acylated chiral 1-(1-naphthyl)ethylamine) that the presence of an amide function and a single asymmetric center is sufficient for the enantiospecific resolution of racemic amides, e.g. *N*-acylamino acid esters, α-methyl-α-amino acid esters, aliphatic *N*-acylamines and α-substituted carboxylic acid amides[83]. Optically active stationary phases have also been synthesized by incorporation of a chiral acyl component in **5**, e.g. (1*R*,3*R*)-*trans*-chrysanthemic acid **6**, *O*-lauroylmandelic acid, and *N*-lauroylproline[84,85], which allow



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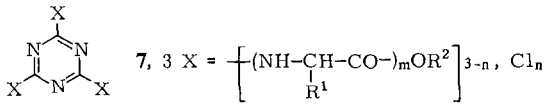
the quantitative resolution of underivatized (±)-menthol, nitrile compounds, *cis* and *trans*-chrysanthemic acid **6**[86,87], macrolide lactones[88] as well as the improved resolution of racemic *N*-TFA amines and carboxylic acid *tert*-butylamides.

In order to improve temperature stability Ôi et al. incorporated the chiral structure elements shown in Scheme 1 into a triazine skeleton **7** via the *N*-terminus[89] and resolved, for instance, proline as the *tert*-butylamide[90], dipeptides (e.g. all four configurational isomers of *N*-TFA-alanylalanine isopropyl ester)[91], *O*-acyl-α-hydroxycarbox-



7, 3 X = $-[(NH-CH(R^1)-CO-)_mOR^2]_{3-n}$, Cl_n

ylic acid esters[92] and underivatized alcohols[93] into their antipodes.

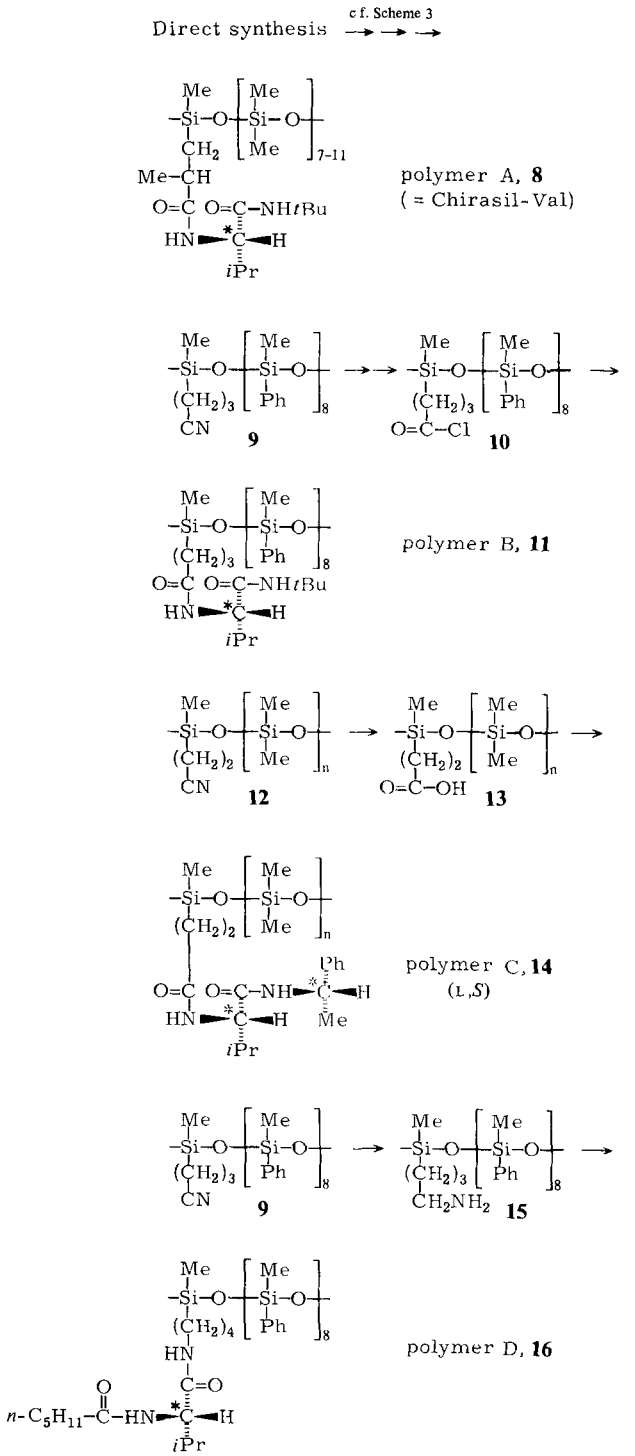
The observation that nitrogen-free racemic *O*-acyl-α-hydroxycarboxylic acid esters could be resolved into their antipodes via hydrogen bonding[92,96,97], led to the development of oxygen-containing, amide-free stationary phases, e.g. di-(−)-menthyl (+)-tartrate for the resolution of racemic *N*-acylamino acid esters, *N*-acylamines and carboxylic acid amides[94]. The results confirmed previous findings of a low degree of chiral recognition between racemic alcohols and didodecyl (+)-tartrate in a gas chromatographic system[95]. Nitrogen-free 2-hydroxycarboxylic acids were also resolved as *O*-TFA alkyl esters on *S*-mandelic acid *S*-α-phenylethylamide[96,97]. The disadvantage of these phases is their low thermal stability. The resolution of racemic, underivatized alcohols on deactivated glass capillary columns, coated with optically active polypropylene glycol (PPG) is remarkable in spite of the low separation factors obtained[98,99].

2.3. Optically Active Polymeric Siloxane Stationary Phases

The employment of low molecular weight stationary phases **1**—**5** (Scheme 1) is limited at high temperatures by thermal decomposition, racemization, and column bleeding. This precludes the resolution of many less volatile racemates in this manner. Only carefully purified amide phases **3** which are modified with long-chain substituents (e.g. R^1 = 1,1-dimethylhexadecyl, $R^2 = n\text{-}C_{21}H_{43}$) can be employed up to 200°C due to their low polarity and volatility[72]. The lower molecular weight stationary phases tend to crystallize at lower temperatures.

A new type of enantiospecific stationary phase was developed by *Frank, Nicholson,* and *Bayer,* where the amino acid amides which form the basis of the low molecular weight diamide phase **3** were attached via the free amino function to the carboxyl group of a polymeric matrix, a statistical copolymer of dimethylsiloxane and (2-carboxypropyl)methyl siloxane, having a high viscosity[100–102]. This stratergy enabled the chemical selectivity of the chiral component L-valine-*tert*-butylamide to be combined with the high thermal stability and involatility of organic polysiloxanes[103].

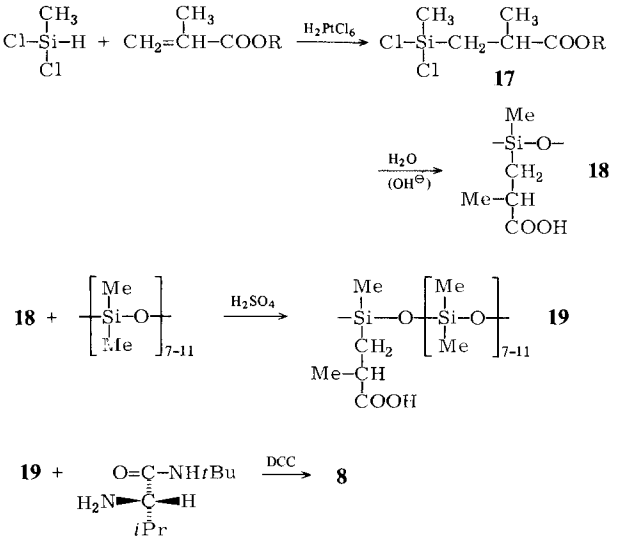
The optically active polymeric siloxane **8** (polymer A, Scheme 2), which is available commercially[104] under the name Chirasil-Val®, is characterized by high thermal stability and low column bleeding and, as a consequence, allows the resolution of enantiomers in temperature programs ranging from 70—240°C. The copolymer component dimethylsiloxane, whose proportion can be varied between wide limits, serves to increase the viscosity and to regulate the mean distance between the chiral side groups; the highest separation factors were observed for a separation of about eleven dimethylsiloxane units[10]. The resolving properties deteriorate with closer spacing because the functionalized polysiloxane tends to crystallize due to the interaction between neighboring peptide side chains. If the spacing is increased, then the cooperative effect between two chiral selectors for enantiomeric discrimination of the selectand begins to decrease. Incidentally, the mean distance bears no relationship to the actual molecular statistical distribution which has been calculated iteratively[105]. This analysis revealed that not all of the chiral centers can contribute to the enantiomer resolution[105]. It ought to be



Scheme 2. Entry to optically active polysiloxanes for gas chromatographic enantiomer resolution.

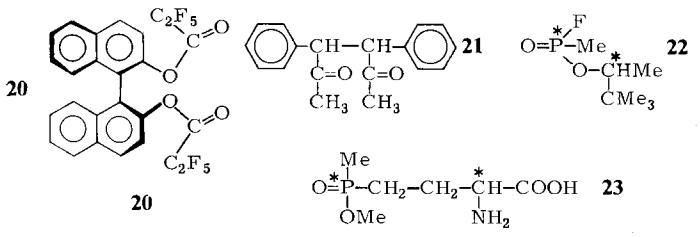
mentioned that Chirasil-Val **8** contains an additional chiral center in the (racemic) side chain.

The synthesis of **8** is outlined in Scheme 3[106]. The coating of deactivated glass capillary columns with **8** enabled the rapid baseline resolution of all 17 racemic protein amino acids for the first time as their *N*-pentafluoropropionyl isopropyl esters[107, 108] (see Fig. 3).



Scheme 3. Four-step synthesis of **8** (Polymer A). 1. Synthesis of the dichlorosilane monomer **17**. 2. Synthesis of the carboxyalkylmethylsiloxane **18**. 3. Synthesis of the copolymer **19**. 4. Coupling of **19** with Val-NH*t*Bu in presence of dicyclohexylcarbodiimide (DCC) to give **8**.—Derivatives of other amino acids and peptides can react analogously with **19**.

Even the analysis of the involatile amino acids Met, Phe, Glu, Tyr, Orn, Lys and Trp does not present any difficulties after suitable derivatization. The analysis of racemic drug metabolites is also possible employing pre-treated glass and, more recently, fused silica capillaries which have been coated with Chirasil-Val **8**[108, 109]. The range of applicability of **8** extends from the resolution of the racemates of aryl glycol esters, atropisomeric binaphthyl derivatives **20**[105], an underivatized diketone (*threo*-3,4-diphenyl-2,5-hexanedione, **21**)[105], alkyl 2-hydroxycarboxylates[110, 111], the nerve gas Soman **22** (four isomers)[112], amino acid sulfoxides[175], and the methyl ester of phosphinotricin **23**[175] which, like **23**, possesses an asymmetric phosphorus atom as well as a chiral carbon atom.



The high thermal stability and the low tendency to column bleeding of Chirasil-Val **8** is of prime importance for combined gas chromatography-mass spectroscopy[175].

The incorporation of phenyl groups[113] and polar modifiers (cf. **24**) in **8** allows the tailoring of the enantiospecificity and polarity of the chiral phase such that all protein amino acids can be resolved quantitatively without peak overlap[114]. (*S*)- or (*R*)-α-phenylethylamine and (*S*)- or (*R*)-1-(1-naphthyl)ethylamine have also been employed as additional chiral components as the amide substituent of L-valine (or L-leucine). The diastereomeric polysiloxane with L-valine-(*R*)-1-(1-naphthyl)ethylamide moieties was able to accomplish a partial resolution of the *O*-TFA derivative of the alcohol 1-cyclopropylethanol[114]. Furthermore, the amine (*R*)-1-(1-naphthyl)ethylamine has been coupled to a polysiloxane and employed to resolve the phenyl or methylurethane derivatives of alcohols into their enantiomers for the first time[114].

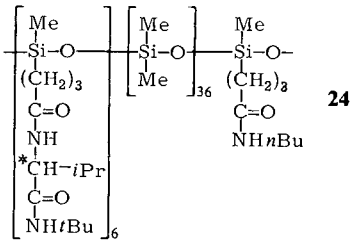
Verzele et al. have described a preparatively simple route to chiral polysiloxanes[115, 116]. Thus, the cyano groups of commercially available polysiloxanes of type **9**[103], e.g. OV-225 or Silar-10C are hydrolyzed and, after conversion into the acid chloride **10**, the carboxyl groups are coupled with the free *amino function* of L-valine-*tert*-butylamide[49] to yield polymeric diamide **11** (Polymer B, Scheme 2). *König* et al. prepared a variant of Polymer B from the commercially available XE-60 polysiloxane **12**, e.g. the diamide **14** (Polymer C, Scheme 2), which, in analogy to modified Chirasil-Val[114], contains (*R*)- or (*S*)-1-phenylethylamine as an additional chiral component in the amide function of the L-valine selector[117–119]. In the case of a diastereomeric selector the relative configurations of the chiral centers is decisive for an optimal enantiomer discrimination and this must be elucidated empirically. Both polysiloxanes **14** (Polymer C (L,*R*) and (L,*S*)) have been synthesized and their complementary resolving power has been compared by means of two capillary columns, each packed with diastereomeric phase[121]. Thus, polymer C (L,*R*) is especially suitable for the resolution of *N*-TFA-amines and *N,O*-bis(TFA)-amino alcohols, while polymer C (L,*S*) can be employed for the resolution of racemic *N*-TFA-amino acid isopropyl esters[9, 120–122]. Polymer C (L,*S*) has also proved valuable for the separation of constitutional and configurational isomers of carbohydrates[117, 118]. Polymer C (L,*S*) has become known as XE-60-L-valine-*S*-α-phenylethylamide[123].

Another synthetic strategy consists of the reduction of the cyano groups of OV-225 **9** with $LiAlH_4$ in diethyl ether and reaction of the resulting amine with the *carboxy function* of *N*-acyl-L-valine (or *N*-acyl-L-leucine) to form the polymeric diamide **16** (Polymer D, Scheme 2)[119]. While in Polymers A—C the macromolecular residue formally constitutes the acyl component, in Polymer D it formally functions as the amide component. Polymer D is particularly suitable for the resolution of racemic *N,O*-bis-acylamino alcohols and *N*-acyl amines[119].

One advantage of the direct synthesis of chiral polysiloxanes of the type **8** lies in the manifold possibilities for variation of copolymer composition, e.g. in the deliberate inclusion of polar modifiers, as in **24**[114].

Commercial polysiloxanes with varying amounts of cyanopropyl groups were employed for the synthesis of polymers B—D[115, 117, 119] which, after hydrolysis and coupling with established chiral selectors, yielded polysiloxanes with similar properties to those of Chirasil-Val **8**[10] or its variants[114]. However, the disadvantage of these pol-

ymer analogues is that the strongly acid or basic conditions necessary for hydrolysis of the cyano groups may also bring about some depolymerization, so that the relationship between the copolymers is uncontrollably altered and hence polarity and viscosity are affected[143]. The acid chloride group in **10** could also cause problems in the preparation of Polymer B, and the depolymerizing properties of $LiAlH_4$ must be taken into account in the synthesis of Polymer D[143].



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Figures 3—5 illustrate typical gas chromatograms featuring analytical enantiomer resolution. Table 2 provides information concerning the classes of compounds, derivatization method, and optically active polysiloxane employed in the gas chromatographic resolution of enantiomers via hydrogen bonding.

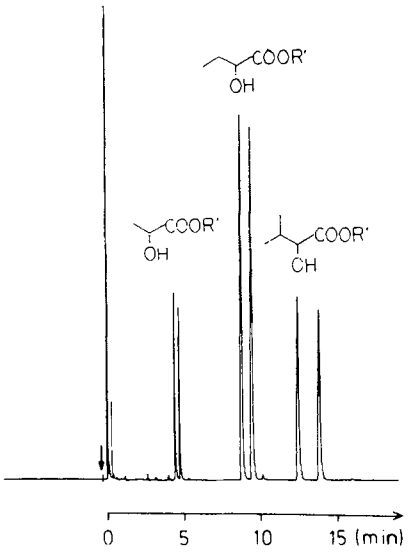


Fig. 5. Enantiomer resolution of racemic α-hydroxy acid esters on Chirasil-Val **8** at 50°C [110]. R'=$CH(C_2H_5)_2$.

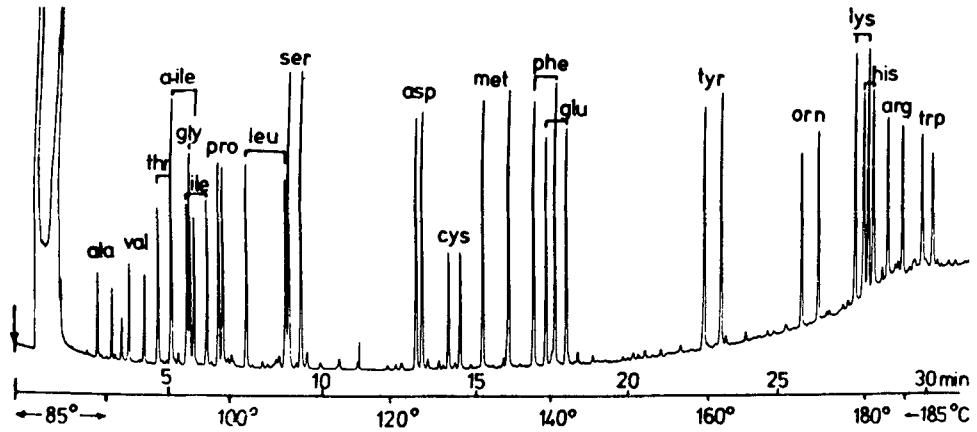


Fig. 3. Resolution of enantiomers of racemic protein amino acids as *N*-pentafluoropropionyl isopropyl esters on Chirasil-Val **8** [175]. OH- and SH-functions were likewise protected with the pentafluoropropionyl group.

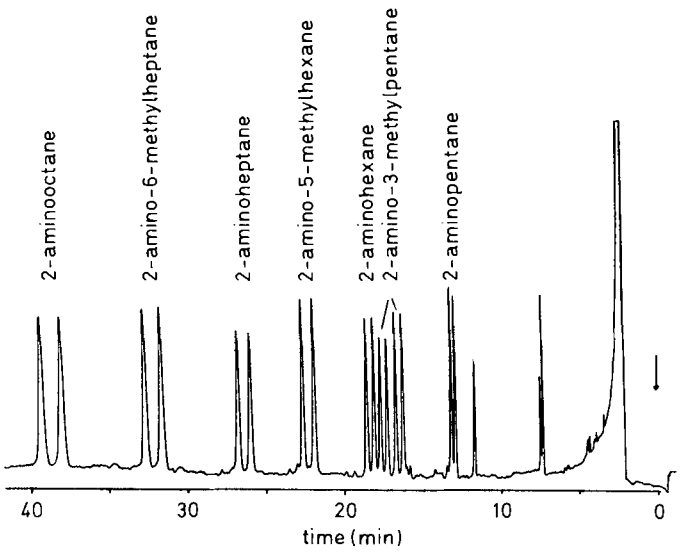


Fig. 4. Enantiomer resolution of racemic amines $RMeHC-NH_2$ as their isopropyl ureas on Polymer C **14** (L,*S*) [125].

2.4. Derivatization Strategies

The gas chromatographic resolution of enantiomers via hydrogen bonding must almost always be preceded by a derivatization of the racemic selectand (cf. Table 2 and [137, 138]). The derivatization is necessary, on the one hand, to transform involatile and/or polar substrates (e.g. amino acids) into derivatives which can be vaporized without decomposition and, on the other, to introduce further chemical functions into the molecule that are capable of forming hydrogen bonds and increasing the chiral recognition of the selector/selectand system. In this way the introduction of a chemically stable amide function can lead to the formation of additional hydrogen bonds with the optically ac-

Table 2. Resolution of enantiomers by gas chromatograhy on chiral polymers A–D (see Scheme 2). A selection of classes of compounds and derivatization.

Class of compound	Derivatization	Polymer	Reference
α-Amino acids	*N*-perfluoroacyl alkyl ester	A, B, C, D	[100, 115, 116, 120, 136]
N-Methyl-α-amino acids	*N*-alkylureido alkyl ester	C(L,*S*)	[124]
Amino alcohols	*N,O-bis*-(trifluoroacetyl)	C(L,*R*), D	[109, 118, 119]
Amines RR'HC–NH_2	*N*-isopropylcarbamoyl	C(L,*S*)	[125]
Amines RR'HC–NH_2	*N*-trifluoroacetyl	C(L,*R*), D	[118, 119, 126]
Hexoses, pentoses	*O*-trifluoroacetyl glycoside	C(L,*S*)	[117, 118, 127]
Hexoses	boronate	A	[128]
Cyclic polyols	*O*-trifluoroacetyl	C(L,*R*)	[126]
α-Hydroxycarboxylic acids	*O*-carbamoyl alkyl ester	A, C(L,*S*)	[111, 125]
α-Hydroxycarboxylic acids	alkyl ester	A	[110]
β-Hydroxycarboxyl acids	*N*-(*tert*-butylcarbamoyl *tert*-butylamide	C(L,*S*), A	[124]
Phenyl glycols	bis(pentafluoropropionate)	A	[105, 109, 175]
Atropisomeric binaphthyls	bis(pentafluoropropionate)	A	[105, 175]
Sulfur-containing amino acids	*N*-pentafluoropropionyl methyl ester	A	[187]
Sulfoxides (methionine-*S*-oxide)	none (perfluoracyl alkyl ester)	A	[147, 175]
sec-Alcohols	urethanes	A, C(L,*S*)	[114, 129]
1,2-Diols, 1,3-diols	cyclic carbonates	C(L,*R*)	[130]
Ketones	*syn, anti*-oximes	C(L,*S*)	[131]
Halocarboxylic acids	amides	A	[188]
Pharmaceuticals	various	A, B, C(L,*R*)	[108, 109, 116, 132–135]

tive selector. The design of an appropriate derivative can also lead to greater detector selectivity or sensitivity (e.g. by element-selective detectors).

The derivatization process should fulfill the following criteria:

1. quantitative reaction;
2. absence of side and rearrangement reactions;
3. exclusion of racemization.

For quantitative analysis, the yield of the derivative and its separation from solvent and derivatizing reagents must be reproducible. It is particularly necessary that derivatization reactions proceed without racemization, if the enantiomeric composition ("enantiomeric excess", *e.e.*) is to be determined gas chromatographically. The proof of absence of racemization is often not easy to perform.

The introduction of thermostable chiral polymer phases has widened the scope of derivatization strategies, since less volatile derivatives can now be analyzed. Thus, the often low separation factors can be compensated at high temperatures by increasing the enantiospecificity between the derivatized selectand and the selector with the advantage of shorter analysis times. Gas chromatographic derivatization methods are well established; recently, derivatization has been automated for quantitative amino acid analysis[139, 140].

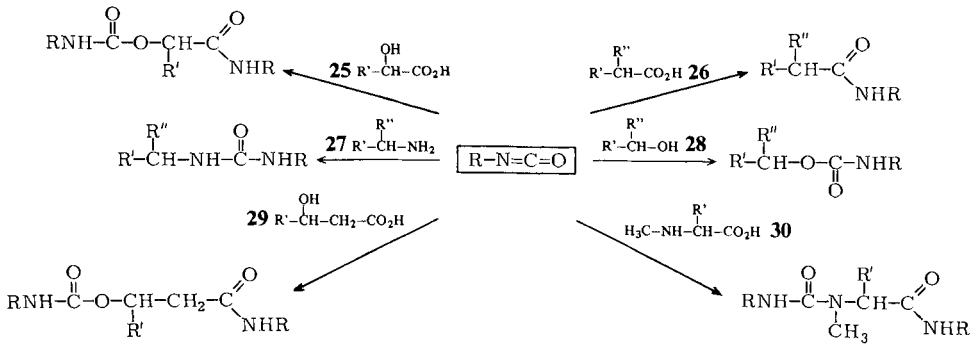
The classical method of derivatization of α-amino acids is their conversion into *N*-perfluoroacyl alkyl esters; OH- and SH-functions are likewise protected with perfluoroacyl groups[44, 46, 50, 52, 141, 142]. The *tert*-butyl esters exhibit the best properties as far as enantiomer resolution is concerned. However, since these are only accessible with difficulty, the isoalkyl esters (e.g. isopropyl esters) are preferred. Trifluoroacetyl (TFA), pentafluoropropionyl (PFP) and heptafluorobutyryl (HFB) are employed as perfluoroacyl residues[54, 142]. TFA derivatives exhibit higher separation factors, while PFP derivatives are more volatile.

The derivatization of α-hydroxycarboxylic acids was first performed by introducing amide functions, e.g. as the *O*-PFP cyclohexylamide for lactic acid[108], or as the *O*-carbamoylalkyl ester[111, 125]. Later resolutions were also achieved with nitrogen-free hydroxycarboxylic acids, e.g. as *O*-acyl esters[92, 96, 118] or even as free alkyl esters[92, 110, 111]. The peak tailing caused by the presence of a free hydroxy group could be suppressed by employing a fused silica capillary column[110]. The conversion of the easily racemizing mandelic acid into the 1-ethylpropyl ester (10% HCl, 110°C, 1 h) proceeded without racemization. In contrast a considerable degree of racemization was observed in the case of mandelic acid during the three-stage derivatization of 2-hydroxycarboxylic acids to *O*-acylated amides[110]. The conversion of the hydroxy groups of 2-hydroxycarboxylic acids into urethane by isocyanate is neither quantitative nor free from by-product formation.

The resolution of acylated secondary alcohols[84, 88, 114] is difficult. An improvement is achieved by chromatography on optically active polymer stationary phases as the urethane derivatives[114, 129]. Phosgene has recently been suggested as a derivatizing agent for 1,2- and 1,3-diols, α-amino alcohols, α-hydroxy acids, and *N*-methylamino acids[130], while isocyanates (see Scheme 4) can be employed to derivatize both functional groups of hydroxy and amino acids simultaneously[144]. The isocyanate method is particularly advantageous for the derivatization of *N*-methyl-α-amino acids **30**, since on acylation these react with complete racemization to yield alkylidene oxazolidin-5-ones[145].

Oximes have been employed for the resolution of racemic ketones[131]. The occurrence of *syn*- and *anti*-isomers may be regarded as a complication. Interconversion of the isomers during separation, which takes place in the case of 2,4-dinitrophenylhydrazones of carbonyl compounds, leading to characteristic interconversion peak profiles[146], has not been observed for oximes. Racemization has also been excluded for enantiomerically pure camphor and fenchone during derivatization to their oximes[131].

For practical purposes enantiomer resolution without resorting to derivatization procedures, as practised in com-



Scheme 4. Isocyanates (R = Me, *i*Pr, *t*Bu, Ph) as derivatizing reagents for α- **25** and β-hydroxycarboxylic acids **29**, 2-alkylcarboxylic acids **26** (each 100°C, 60 min), amines **27** (20°C, 30 min), *sec*-alcohols **28** (100°C, 10 min), and *N*-methyl-α-amino acids **30** (100°C, 60 min) [144].

plexation gas chromatography[2, 11], is advantageous. Only in isolated instances have underivatized selectands, e.g. 1-phenyl-2,2,2-trifluoroethanol[93], 3,4-diphenyl-2,5-hexanedione **21**[105], sulfoxides[147], barbiturates[132] and photodimers of cycloalkenones[148], been resolved on dipeptide phases and chiral polysiloxanes. The separation factors are often very small since no suitable functions are available for strong hydrogen bond formation. Complexation gas chromatography, which was designed following the realization that many racemic selectands do not possess functions suitable for derivatization (e.g. ethers, esters, lactones, unsaturated hydrocarbons) is particularly suitable for the resolution of underivatized alcohols and ketones[22] (see footnote [**] on page 747).

2.5. Thermodynamic Parameters of Gas Chromatographic Enantiomer Resolution

Gas chromatography retention parameters are an important source of data for the calculation of thermodynamic association constants of molecular complexation (see the literature cited in [23] and [149]). The difference in the free enthalpy of association for an enantiomer pair— $-\Delta_{R,S}(\Delta G^\circ)$ can be calculated from the difference in the association constants for the antipodes of the selectand and the chiral selector according to Eq. (1) (*R* refers arbitrarily to the later and *S* to the earlier eluting enantiomer, respectively):

$$-\Delta_{R,S}(\Delta G^\circ) = RT \ln K_R/K_S \tag{1}$$

The difference between the free enthalpies of association of selectands, which are resolved via hydrogen bonding with dipeptide and polysiloxane stationary phases, can be calculated from the difference in retention of the enantiomers via the separation factor α_{max}[50, 80, 81]:

$$-\Delta_{R,S}(\Delta G^\circ) = RT \ln(t'_R/t'_S) = RT \ln \alpha_{max} \tag{2}$$

The separation factor α_{max} represents the relationship between the net retention time t' (measured from the air or methane peak, t_M = dead time) of the more strongly and more weakly retained enantiomer. Since the net retention time is determined by both the physical *and* the chemical contributions to retention, the decisive chemical contribution of the enantiomer differentiation $-\Delta(\Delta G^\circ)$ is generally underestimated when using Equation (2). When a selector is used that is only partially optically enriched then knowledge of the degree of enantiomeric purity (*e.e.*) can be employed to obtain the maximum separation factor valid for quantitative enantiomeric purity by mathematical extrapolation[50].

The temperature dependence of the separation factor α_{max} can be employed to calculate the Gibbs-Helmholtz parameters $-\Delta_{R,S}(\Delta H^\circ)$ and $\Delta_{R,S}(\Delta S^\circ)$ of chiral recognition according to Eq. (3) and (4):

$$R \ln \alpha_{max} = -\frac{\Delta_{R,S}(\Delta H^\circ)}{T} + \Delta_{R,S}(\Delta S^\circ) \tag{3}$$

$$\left(\frac{\partial \ln \alpha_{max}}{\partial (1/T)}\right)_p = -\frac{\Delta_{R,S}(\Delta H^\circ)}{R} \tag{4}$$

According to Equation (3) a plot of $R \ln \alpha_{max}$ against $1/T$ is linear, whose slope is the difference between the enthalpy of association and whose intercept is the difference of the entropy of association of the highly dilute enantiomers in the stationary phase. The lower limit for enantiomer differentiation, which still yields complete peak separation in a high-performance capillary column can be estimated as 10 cal/mol for $-\Delta_{R,S}(\Delta G^\circ)$ corresponding to a separation factor $\alpha = 1.01$ at 25°C[7].

Values of $-\Delta(\Delta G^\circ)$ in the range 40—580 cal/mol were measured for the gas chromatographic resolution of *N*-TFA-2-amino alkanes on the "ureide" phase **4** (Scheme 1)[80]. As would be expected a linear relationship was observed between $\ln\alpha$ and $1/T$ for the resolution of the enantiomers of *N*-perfluoroacylnorleucine alkyl esters on the dipeptide phase *N*-TFA-phenylalanyl-L-leucine cyclohexyl esters[47]. The Gibbs-Helmholtz parameters of the enantiomer discrimination between racemic *N*-TFA-alanine and leucine esters and the diamide phase **3**, $R^1 = n\text{-}C_{11}H_{23}$, $R^2 = CH_2tBu$, have been determined[150]. The highest values for the selectand *N*-TFA-leucine (1-ethylpropyl ester) were $\Delta(\Delta H^\circ) = -1.611$ kcal/mol, $\Delta(\Delta G^\circ) = -338$ cal/mol, and $\Delta(\Delta S^\circ) = -3.32$ cal mol^{-1} K^{-1} at 110°C.

When chiral polysiloxanes are employed as stationary phases for enantiomer resolution the physical contribution of the achiral polymer network to the net retention time t' cannot be ignored. Otherwise, the actual contribution of the chiral side chain to enantiospecificity as calculated

from the ratio t'_R and t'_S will be underestimated. The separation of the physical and chemical contribution to the retention time can be attempted by employing a polysiloxane reference column (e.g. SE 30)[105].

The temperature dependence of the retention times of racemic aromatic diol diesters has been studied in order to determine the thermodynamic data for enantiomer discrimination on Chirasil-Val **8** (Polymer A)[105]. Enthalpy parameters were obtained from the approximation equation (5) (t' = net retention time, t_M = dead time):

$$\frac{\partial(\ln t')}{\partial(1/T)} - \frac{\partial(\ln t_M)}{\partial(1/T)} = -\frac{\Delta H^\circ}{R} \tag{5}$$

For gas chromatographic enantiomer resolutions reported up to now, a decrease in the separation factor α has always been observed on increasing the temperature. Since the separation factors are linked to changes in the free enthalpy of association, and the latter depends on the interplay between enthalpy change, entropy change, and temperature [Eq. (6)] according to the Gibbs-Helmholtz equation, at very high temperatures the separation factors may, in principle, increase again with simultaneous reversal of the order of elution[105].

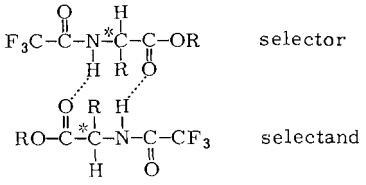
$$-\Delta_{R,S}(\Delta G^\circ) = -\Delta_{R,S}(\Delta H^\circ) + T\Delta_{R,S}(\Delta S^\circ) \tag{6}$$

Thus, the determination of the Gibbs-Helmholtz parameters provides a criterion for a more precise understanding of the mechanisms of chiral recognition. Gas chromatography constitutes an important tool (which has only been employed in isolated instances) for a deeper insight into the mechanisms and origins of enantiospecificity, which is a common phenomenon in living matter, with preference for the image over the mirror image.

2.6. Mechanistic Aspects of Gas Chromatographic Enantiomer Resolution via Hydrogen Bonding

The design of the first selector/selectand system for the gas chromatographic resolution of enantiomers on the basis of simple amino acid entities was inspired by the known stereospecificity of enzymes[4]. The observed enantiomer discrimination was attributed to the formation of diastereomeric associates between the racemic selectand and the optically active selector[12,40]. In their first interpretation *Feibush* and *Gil-Av* suggested that association complexes were formed rapidly and reversibly by hydrogen bonding between carbonyl and amide functions[44] (Scheme 5).

Depending on the configurations of the selector and the selectands, complexes possessing differing stabilities are



Scheme 5. Hydrogen bonding between selector and selectand.

produced during combination to diastereomeric associates. This thermodynamic expression of the enantiomer discrimination, caused by chemical selectivity, depends on a rapid establishment of the chemical equilibrium. This condition is fulfilled for hydrogen bonding even when preequilibria are involved[105].

A kinetic control of the enantiomeric resolution process can also be envisaged and could be recognized, on the one hand, by peak broadening and, on the other, by dependence of the retention time on the flow rate of the mobile phase.

Such effects have apparently been observed when liquid-crystalline stationary phases were employed[81,82]. The sharp peak elution observed in the overwhelming number of cases allows the exclusion of kinetic effects.

While only two hydrogen bonds can be formed in the association of *N*-TFA-amino acid alkyl esters with phase **1**, phases **2**—**4** can enter into a further association (due to the presence of an additional amido function (cf. Scheme 1).

The order of elution of amide and amino acid derivatives on "ureide" phases has been interpreted by *Feibush* et al.[27] by employing the *Cram* model, in which the steric requirement of the substituents (l > m > s) at the asymmetric center is employed to explain enantiospecificity.

Enantiospecific interactions other than hydrogen bonds can also lead to enantiomer discrimination. Thus *Stölting* and *König*[64] observed a racemate resolution of *N*-TFA-proline esters on *N*-TFA-L-prolyl-L-proline cyclohexyl ester as stationary phase, a selector/selectand system which does not possess amide hydrogens capable of hydrogen bonding.

The original model of a dimeric association complex, comprising three hydrogen bonds[47], was abandoned by *Beitler* and *Feibush*[50] in a systematic investigation of the variations of residues R^1 and R^2 in the diamide phase **3**. More recent models take into account the common knowledge of the structure and conformation of peptides[4,69]. Assuming a planar *trans*-conformation **31** for the amide function, diamides at high dilution can form a planar five-membered ring (C_5 unit) or a puckered seven-membered ring (C_7 unit) by intramolecular hydrogen bonding (see **32**).

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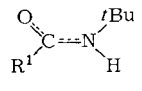

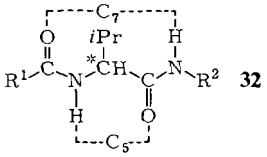

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However, under the conditions of a gas chromatographic experiment oligomerization by intermolecular hydrogen bonding with the formation of "C_5–C_5", "C_7–C_7" and "C_5–C_7" associates is assumed in the molten diamide (cf. Fig. 6).

The β-pleated sheet structure of peptides constitutes a typical example of this interaction. According to Figure 7 associates of ring size 5 + 5 = 10 and 7 + 7 = 14 are formed when the chains are arranged parallel; antiparallel arrangement leads to associates of ring size 5 + 7 = 7 + 5 = 12. Numerous spectroscopic and structural investigations on

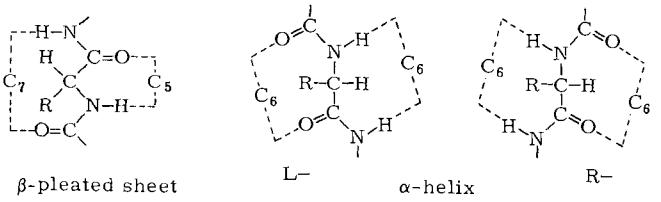


Fig. 6. Bifunctional coordination possibilities for hydrogen bonding in peptides [105].

N-acyl-α-amino acid alkylamides have confirmed these association mechanisms. It is important to note that (under the conditions of the gas chromatographic experiment) the preferred structure of the diamide in the crystalline state is largely preserved in the melt.

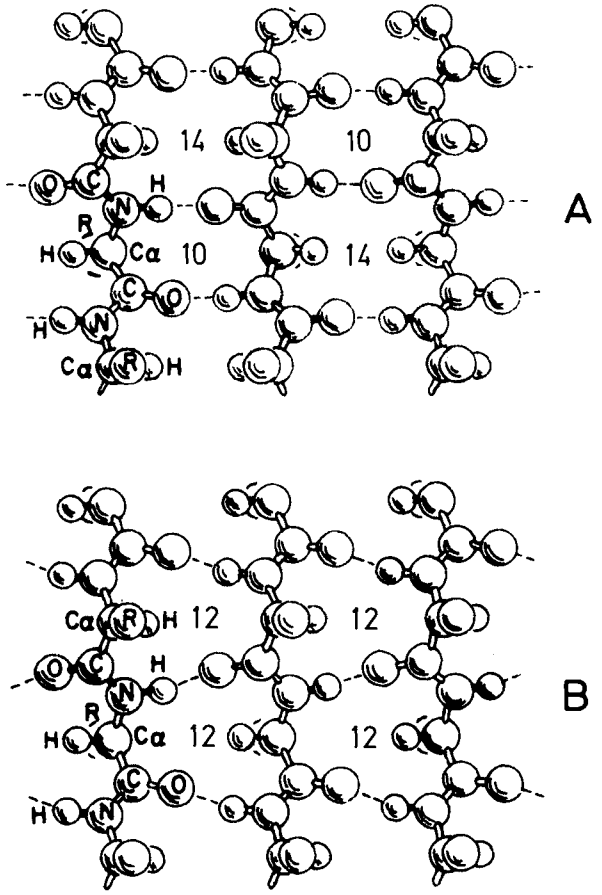


Fig. 7. β-Pleated sheet structure of polypeptides (A: parallel chains, B: antiparallel chains) [78]. The numbers signify ring size.

According to *Beitler* and *Feibush*[50], a selectand molecule associates with a diamide selector via two hydrogen bonds forming a $5+5=10$ ring in an analogous manner to the β-pleated sheet structure of polypeptides (cf. Fig. 8). The differing positions of the isopropyl group of valine in the diamide phase and the amino acid residue R^3 of the selectand in the diastereomeric associates L,L′ and L,D′ may explain the observed enantiospecificity, whereby it has been demonstrated experimentally that the L,L′ combination is more stable than the L,D′ one[50]. Later, an association by means of $7+7=14$ rings was postulated to explain

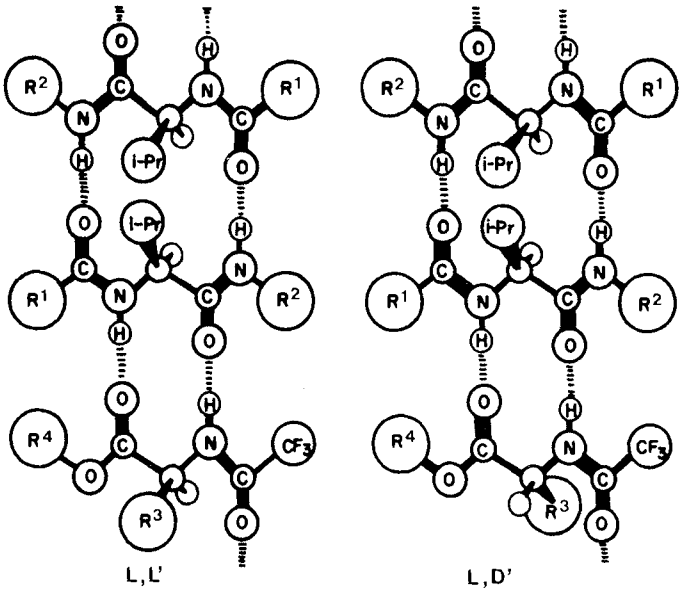


Fig. 8. The mechanism of association between amino acid derivatives and diamide phases [50].

the association of the *N*-TFA isopropyl ester of an L-α-amino acid with the diamide *N*-acyl-L-leucine-*tert*-butylamide and analogues (Fig. 9)[78]. Here too the differing steric situation of the residue R and the isobutyl group, which are aligned parallel in the case of amino acids of the same configuration, leads to differing stability for the associate and is assumed to be responsible for chiral recognition. All amino acid derivatives which possess a primary amino group (except proline) are resolved into their enantiomers by the same mechanism since the elution of D- and L-form is identical in all cases (see Section 2.7).

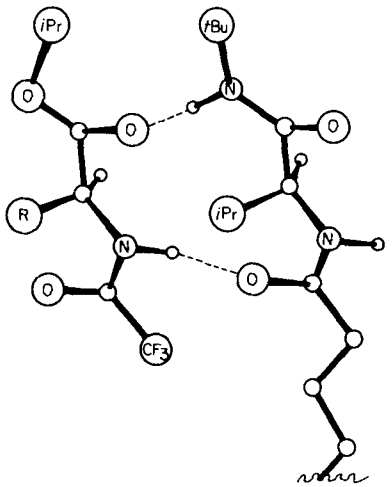


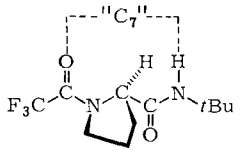
Fig. 9. Association of *N*-TFA amino acid isopropyl esters and a diamide of type **3** [78].

This model is able to explain the following experimental results[78a]:

1. The diamide phase *N*-lauroyl-*N*-methyl-L-leucine-*tert*-butylmethylamide, which does not possess any free am-

ide functions, does not exhibit any enantiospecificity for amino acid derivatives. This underlines the importance of hydrogen bonding for enantiospecificity.

2. Proline is intrinsically incapable of forming more than one hydrogen bond and, hence, is very difficult to resolve into its enantiomers. The transformation of the carboxy group to an amide **33**[75,90], however, allows an effective resolution of the enantiomers because of the presence of a C_7 unit[78a].



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3. Only the *N*-terminal amino acid of dipeptide phase **2**[44] is capable of forming a "C_7" unit with associating selectands. Indeed, the *C*-terminal amino acid does not participate in enantiomer discrimination[67,68].

Since models only reflect the major part of an experimental finding, other association mechanisms can also come into play. For example, association by acyclic hydrogen bonding, van der Waals interactions, and dipole dipole interactions can also be considered. The multiplicity of possible enantiospecific selector/selectand interactions is clearly demonstrated by the resolvability of *N*-TFA-proline esters and *N*-acylamines[73], of 2-hydroxycarboxylic acid alkyl esters[96], and α-chlorocarboxylic acid amides[77] on diamide phases.

Apart from 1:1 association complexes there is also the possibility of 1:2 interaction, whereby the selectand, which is employed at great dilution, is sandwiched between two molecules of the undiluted selector which is present in large excess in the stationary phase. Such intercalation interactions have been postulated for amide phases of structure **5** (Scheme 1)[83]. According to Figure 10 the selector (*R*)-*N*-lauroyl-1-(1-naphthyl)ethylamine crystallizes with the formation of intermolecular hydrogen bonds along a 5-Å translation axis[150]. The parallel arrangement of the aromatic rings and the linearity of the alkyl side chains which are also retained in the melt are important structural features. The constitutionally and configurationally equivalent selectand (*R*)-*N*-TFA-1-(1-naphthyl)ethylamine fits ideally into this structure, while the intercalation of its enantiomer is more difficult. Hence, the gas chromatographically observed enantiospecificity can readily be attributed to the differing stability of the diastereomeric intercalation aggregates, which has been additionally confirmed by calculations of energy data[83,150].

The interpretation of the enantiospecificity of optically active polysiloxanes (Polymers A—D) must take into account both the (statistical) distance between the chiral side chains and the preferred conformation of the amino acid selector. According to statistical evaluation of valine residues in polypeptides and theoretical calculations valinamide exists preferentially in a β-pleated sheet type structure or α-helical form with a preference for the latter conformation[105,175].

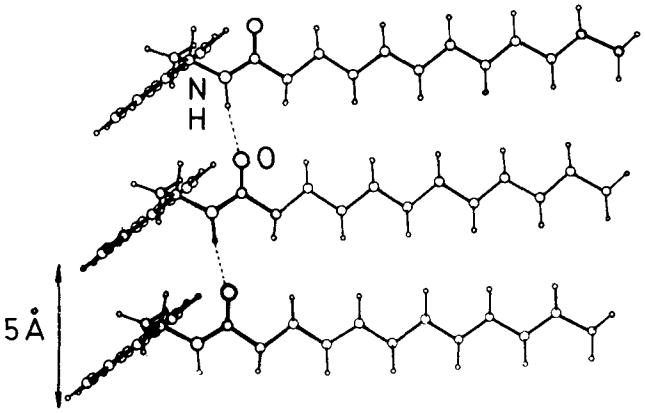


Abb. 10. Hydrogen bond formation along a 5-Å translation axis in (*R*)-*N*-lauroyl-1-(1-naphthyl)ethylamine (*R*)-**5** [150].

According to *Koppenhöfer*[105] the observed enantiospecificity of Chirasil-Val **8** for bifunctional oxygen-containing selectands containing no amide functions can, according to Figure 6, onl occur with a conformation of the valinamide selector in which both amide groups are directed towards the substrate (α-helix type), while a β-pleated sheet structure is to be expected for nitrogen-containing selectors[175].

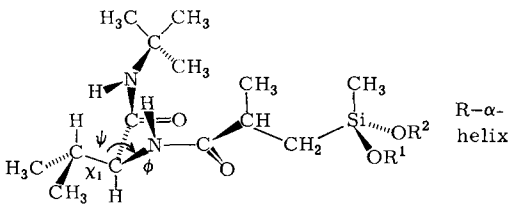


Figure 11 illustrates the postulated β-pleated sheet structure of an associate between Chirasil-Val and intercalated *O*-pentafluoropropionyl-L-lactic acid cyclohexylamide[108], which is characterized by the formation of the maximum number of hydrogen bonds. According to this model for the L,L′ combination the bulky isopropyl groups of **8** and the methyl groups of the lactic acid derivative are stacked in layers one above the other and stabilize the associate by

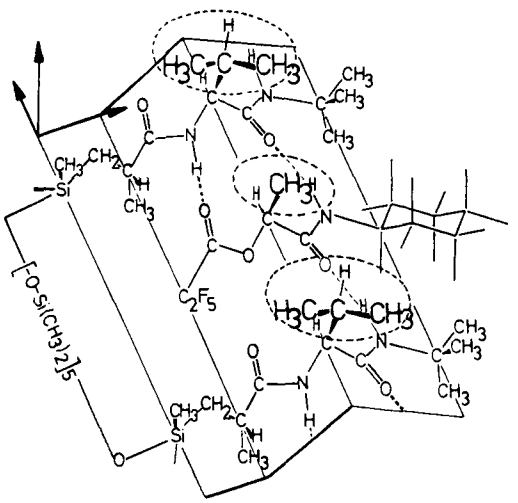


Fig. 11. β-Pleated sheet structure of an associate of Chirasil-Val **8** (Polymer A) with *O*-pentafluoropropionyl-L-lactic acid cyclohexylamide [108].

van der Waals forces[108]. The L,D′ combination does not allow of such a layer formation. The model also takes into account the importance of the main polysiloxane chain which separates the L-valinamide side chains.

These models assume that different conformations of the valinamide selector are required by nitrogen-containing and nitrogen-free selectands. This implies either that Chirasil-Val exists in various conformations or that a preferred conformation is induced during the "diastereotropic"[111] approach of selector and selectand.

2.7. The Correlation between Absolute Configuration and Retention Properties

The large degree of agreement between the retention properties of individual enantiomers of selectands with respect to their absolute configuration within an homologous series constitutes one of the significant characteristics of gas chromatographic selector/selectand systems. The correlation of absolute configuration with order of elution has acquired a place of great importance in enantiomer analysis. The basis for such correlations is the overwhelming analogy between the separation mechanism for structurally similar substrates on selectors of defined chirality.

Early on *Gil-Av* et al.[12] demonstrated that all the D-*N*-TFA-α-amino acid esters investigated eluted before their L-enantiomers on stationary phase **1**, if the selector possesses the L-configuration. As expected the order of elution is reversed if the mirror image D-stationary phase is employed (peak inversion). Likewise, the D-derivatives are eluted before L-*N*-TFA-amino acid esters on L-valine diamide phases regardless of whether the diamide is present in low molecular weight[50] or polymeric form (Polymers A, B, C, Scheme 2)[100, 115, 120]. The order of elution of β and γ-amino acid derivatives is, however, the reverse of that for α-amino acids on *N*-lauroyl-L-valine (1-pentylhexyl)amide[50].

A systematic investigation of the retention behavior of *N*-TFA amines and *N*-TFA α, β and γ amino acid esters on the "ureide" phase **4** revealed[27] that the order of elution and the separation factors depend on the steric requirements of the substituents at the asymmetric carbon atoms of the selectands. The substituents were ordered according to their effective size without taking any account of their chemical function in analogy to *Cram*'s model. If the substrate model is viewed from the asymmetric carbon atom in the direction of the nitrogen atom, then the substituents are arranged in decreasing size in either a clockwise or counterclockwise direction. All enantiomers whose substituents are arranged clockwise in this classification are eluted as the second peak on the L,L′ phase. The size of the separation factor α increases with increasing size difference of the substituents. This rule, which correlates the configuration with the order of elution, has been confirmed by many observations: Since the size of the substituents R and CO_2R' is reversed, D-*N*-TFA-alanine alkyl esters are eluted before the L-enantiomers while L-*N*-TFA-leucine methyl esters are eluted before the D-isomers; the separation factors become smaller as the effective size difference between R and CO_2R' decreases or become proportionally larger with a corresponding increase[27]. The correlation between configuration and retention behavior in gas chromatography has enabled a controversy to be resolved without resort to chiroptical methods[28] concerning the absolute configuration of 2-amino-3-methylbutane and 2-amino-4-methylbutane.

Derivatized amines, alcohols, ketones, hydroxycarboxylic acids and amino acids also exhibit consistent retention properties with respect to their absolute configuration on optically active polysiloxanes[10, 97]. In analogy to the differing separation mechanisms for nitrogen-containing and nitrogen-free selectands on Chirasil-Val (Polymer A), 2-hydroxycarboxylic acids exhibit varying retention relationships depending on the derivatization strategy. Thus the L-enantiomers of 2-hydroxycarboxylic acid alkyl esters are eluted before those with the D-configuration on Chirasil-L-Val, while the order of elution is reversed for the corresponding amides or urethanes[110, 111].

Needless to say, the correlation between molecular configuration and retention behavior of selectands in conjunction with the absolute configuration of the selector constitutes an important criterion for the mechanistic consideration of chiral recognition.

2.8. Applications of the Gas Chromatographic Method to the Resolution of Enantiomers

The suitability of gas chromatography for sensitive and precise determinations of enantiomer compositions[2] was recognized by several research groups after the first successful *quantitative* separation of amino acid derivatives and employed for many types of investigations, e.g. the demonstration of unnatural amino acids in bacterial cell walls and in peptide antibiotics, the monitoring of amino acid purity during peptide synthesis, the determination of the degree of racemization during peptide hydrolysis, the dating of paleontological and archeological finds by exploiting the time-dependence of amino acid racemization, the search for biogenic amino acids in extraterrestrial material, and the amplification of optical activity under abiotic conditions[4, 10, 14, 151, 175].

Thus a D/L ratio of up to 2.33 was observed gas chromatographically for alanine from the cell walls of staphylococci[152], and isovaline (2-amino-2-methylbutyric acid) from various peptide antibiotics could be assigned to the *R*-configuration[157]. During the hydrolysis of the dodecapeptide $(Leu\text{-}Ala)_6$, which had been synthesized by the *Merrifield* solid state method[153], less than 0.1% of unnatural amino acid antipodes could be detected, whereas the racemization of L-asparagine during the hydrolysis of the heptadodecapeptide desamidosecretin amounted to up to 2%[153]. By gas chromatography, it was also possible to demonstrate precisely the high optical purity of the amino acids of peptides synthesized according to the four component condensation reaction of *Ugi*[154]. Gas chromatographic methods have also been employed for the systematic stereochemical analysis of various peptide antibiotics (antiamoebin I, emerimicin, alamethicin I, II)[158, 159, 160].

The racemization of amino acids in living cells, which do not exhibit renewal processes, is of importance in the

study of ageing phenomena. The racemization of amino acids in dead, fossilized materials can be employed as a dating parameter. Knowledge of the effect of temperature, time, humidity, and other environmental conditions on the rate of inversion of natural amino acids is hence of great importance for gerontological, geochronometric (paleotemperature profiles), and archeometric investigations.

As a reversible first order reaction the rate constant for the inversion of amino acids can be determined from the following equation when using optically pure starting materials[161],

$$k = \frac{1}{2t} \cdot \ln \frac{\text{L}+\text{D}}{\text{L}-\text{D}}$$

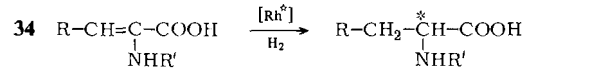
where L and D are the concentrations of the enantiomers determined gas chromatographically by peak area comparison at time t. As expected when plotted against $2t$, $\ln[(\text{L}+\text{D})/(\text{L}-\text{D})]$ yields a straight line passing through zero whose gradient corresponds to the rate constant k.

There is a great interest in the detection of organogenic material in interstellar space. If there were to be any preference of the image over the mirror image, it is to be expected from terrestrial evidence that this would involve biogenic material. In the case of meteorites the demonstration of racemic amino acids is an indication of either abiotic origins or of very great age, while the detection of L-amino acids can be attributed to terrestrial contamination. Investigations of the Murray and Murcheson meteorite and comparison with urban earth samples suggest considerable terrestrial contamination with L-amino acids[162]. No D,L-amino acids could be demonstrated gas chromatographically at the detection limit of 0.1 ppm in the Apollo moon samples[163]. Incidentally, this result eliminates the possibility of a terrestrial contamination of the carefully isolated samples from the lunar Sea of Tranquility. An interesting archeometric investigation was concerned with the determination of the D,L-asparagine ratio in parchment from the Dead Sea Scrolls, which provided information concerning the date of the degradational transformation of the collagen to gelatine[164, 165].

The gas chromatographic method of determining enantiomer composition is particularly suited to investigations concerned with the laboratory simulation of the origin of optical activity. Since only slight deviations from the racemic composition would be expected in such cases, the unbiased employment of polarimetric measurements may lead to grave misjudgements. In a gas chromatographic analysis employing diamide phase **3**[166], *Bonner* et al. were able to demonstrate small amounts of enantiomer enrichment (up to *e.e.* 2.5%) in the abiotic kinetic resolution of leucine[151]. It was demonstrated in preliminary experiments that the gas chromatographic method employing high performance capillary columns and digital peak integration yielded an accuracy and precision of 0.03%—0.7% absolute error and a standard deviation of 0.03%—0.6% with leucine mixtures of known enantiomeric composition[166]. Furthermore, the results were verified by the use of stationary phases with the opposite chirality. This strategy allows the recognition of a falsification of the analytical data by co-eluting (achiral) impurities, since a peak inversion only takes place with optical isomers[167].

The application of gas chromatographic enantiomer analysis in the field of enantioselective synthesis has recently been the subject of a detailed review[2]. It was pointed out that this reliable method finds astonishingly little employment in work claiming "quantitative enantiomeric purity". The determination of enantiomeric purity by polarimetry applying the criterion of optical purity may involve errors[2] and the employment of nuclear resonance methods with the aid of chiral shift reagents usually allows the determination of enantiomeric purity to about *e.e.* 97%.

The hydrogenation of dehydroamino acids **34** to amino acids in the presence of optically active rhodium complexes is an important asymmetric homogeneously catalyzed, reaction[168].



Gas chromatography has only been employed occasionally for the precise determination of the enantiomeric yield of the amino acids so produced[169, 170]. The enantiomeric yield for *N*-acetylphenylalanine, which has been underestimated in polarimetric determinations because the maximum optical rotation reported in the literature is too high, has been corrected by gas chromatographic methods and the correct specific rotation α_{max} obtained by extrapolation[171, 172]. For investigations concerning the homogeneously catalyzed, enantioselective synthesis of dipeptides by "double asymmetric induction"[173, 174], the chiral stationary phase described by *Ôi* et al.[91] can be employed to determine not only their diastereomeric composition but also the enantiomeric purity.

The introduction of thermally stable polymeric stationary phases (Polymers A—D, cf. Scheme 2) into gas chromatographic enantiomer analysis[175], and their commercialization[104, 123], had the effect of opening up a broad range of potential applications for a wide range of users. The suitability of the polymeric phases for GC-MS coupling due to their low rate of bleeding is worthy of special mention[176]. The employment of the SIM (selected ion monitoring) technique can bring about a further considerable increase in sensitivity and substrate selectivity.

Frank, Nicholson, and *Bayer*[178] have developed a complementary approach to amino acid analysis[139 140] by means of the "enantiomer labeling" method. Here the unnatural D-amino acid is employed as an internal standard[177, 178, 179] for the quantification of the L-enantiomer. Since the enantiomers possess identical (nonchiroptical) properties in an achiral environment, the enantiomeric ratio is neither affected by sample manipulation (isolation, derivatization, fractionation) nor by gas chromatographic manipulations (dilution of sample, injection, splitting, detection). Thermal or catalytic decomposition, loss of substance, incomplete isolation, and semiquantitative derivatization are all without effect on the analytical result. It is unnecessary to calibrate the detector, but detector response must be linear over a wide concentration range, a

requirement that is fulfilled by flame ionization detectors[105].

The method of enantiomer labeling presupposes a precise knowledge of the enantiomeric purity of both the sample and the standard, which must be determined separately[178]. The concentration of a racemate can also be measured by this method by employing an enantiomerically pure standard, just as can an enantiomerically pure substrate with a racemic standard. The method has been proposed for the precise determination of the chemical yield in enantioselective syntheses[2], whereby a known quantity of optically active standard is admixed with the reaction mixture (or an aliquot therefrom) and the amount of product is calculated from the change in enantiomeric composition before and after addition. This method is useful for enzymatic reactions, for instance, where the amounts of reaction products are so small that they cannot be isolated without losses.

The employment of optically active polysiloxane phases for the resolution of the enantiomers of various classes of compound (see Table 2) has led to important applications, e.g. investigations of amino acid racemization during peptide synthesis and hydrolysis. *Frank, Woiwode, Nicholson* and *Bayer*[180] investigated the rate of acid-catalyzed racemization of all the proteinogenic amino acids and differentiated between the rates of inversion of bound and free amino acids. Furthermore, with the aid of deuterium labeling and coupled GC-MS[176] it was possible to distinguish between the amount of unnatural amino acid originally present and the amount produced on hydrolysis[181] since the incorporation of deuterium is only to be expected on inversion of configuration.

The investigations of biological fluids, forensic chemistry, pharmaceuticals and therapeutics are important fields for the application of gas chromatographic enantiomer analysis[132, 133, 175, 176, 182–185], as is also the configurational analysis of polysaccharides[186].

It is to be expected that, in the future, gas chromatography will become established as one of the standard methods for the reliable enantiomeric analysis of volatile chiral compounds.

3. Summary and Outlook

Enantiospecific selector/selectand systems have been described which allow a quantitative gas chromatographic enantiomer resolution. Advances in glass and fused silica capillary column technology in combination with the development of thermally stable chiral polysiloxane phases and the employment of improved derivatization strategies has led to an extension of gas chromatographic enantiomer resolution to many classes of compounds. The polymeric phases are especially suitable for temperature programming and for the coupling of gas chromatography and mass spectroscopy. The method of "enantiomer labeling" permits the reliable quantification of enantiomers in biological fluids, of chiral pharmaceuticals, in forensic chemistry and of the products of enantioselective transformations. Gas chromatography provides unequivocal results in the determination of the enantiomeric composition (*e.e.*, enantiomeric excess) particularly in the boundary regions of slight enantiomeric excess (deviations from racemic composition) and high enantiomeric purity (detection of traces of the other enantiomer).

The large body of data on enantiomer resolution by gas chromatography allows a deliberate choice of selector/selectand systems for the detailed investigation of the molecular mechanisms of chiral recognition and of the correlation of the influence of the structural factors of selector and selectand on the enantiospecificity. The order of elution is constant within wide limits for analogous and homologous selectands. For this reason gas chromatography can be employed for the determination of absolute configuration without knowledge of chiroptical properties. The use of optically active phases of opposite configuration can confirm or exclude the enantiomeric origin of a peak separation.

For future development in chromatographic enantiomer separation it seems likely that GC and LC (HPLC) will complement each other and each method will find its own particular range of applications. Whereas preparative separation is of interest in LC, the main application of GC will be in enantiomer analysis. GC can be employed to resolve the enantiomers of many components simultaneously within a short time (e.g. amino acid analysis) and complications associated with the nature of the mobile phase are largely unknown. GC readily lends itself to automation.

It is surprising that all the GC systems known today are characterized by small separation factors in comparison with those obtained in LC. This, however, is not a practical disadvantage since together with the high separating performance, particularly of capillary columns, it allows in this way acceleration of the analysis and substances in mixtures can be resolved without peak overlap. The present enantiospecific selector/selectand systems of gas chromatography, however, seem quite unsuitable as models for stereospecific enzymes. Hence, the optimization of such systems remains a stimulating aim for the future. In particular the employment of alternative principles of chiral recognition, that are known in nature, will increase in importance. Mention should be made of enantiomer resolution on phases with host-guest interaction in chiral cavities *via* molecular inclusion, which has already been initiated employing cyclodextrin phases.

Besides hydrogen bonds, other intermolecular forces, or combinations thereof, can also be considered for the resolution of enantiomers by gas chromatography, e.g. charge transfer interactions and ionic and dipole-dipole attractions. The resolution of enantiomers by complexation gas chromatography based on the enantiospecific coordination interaction often yields high separation factors.

Preparative enantiomer resolution is possible by gas chromatography, too. The amounts isolated are small, however, but are suitable for the determination of chiroptical properties or for the correlation of configuration or determination of biological activity.

As far as the employment of commercially available enantiospecific stationary phases is concerned, the user must distinguish between the factors availability, performance, reproducibility and stability. The inspection of chromato-

grams, in so far as they are available, often provides decisive information.

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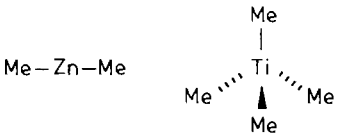
Photochemistry of Alkyltransition-Metal Complexes

By Helmut G. Alt*

Alkyltransition-metal complexes play an important role in catalytic processes (e.g. Ziegler-Natta low-pressure polymerization, hydroformylation, Fischer-Tropsch synthesis), in the biochemistry of humans and animals (e.g. coenzyme B_{12}), and in the classical theory of the chemical bond (e.g. multicenter bonding). The chemistry of alkyltransition-metal complexes is 30 years old, but only with the '70s came the understanding necessary for the systematic synthesis of thermally stable representatives of this class of compounds by blocking preferred decomposition pathways—e.g. β-hydrogen elimination—by the introduction of suitable ligands. In this article it is shown that thermally stable alkyltransition-metal complexes can be dealkylated under mild conditions (even at 12 K) with the help of UV light, thus producing highly reactive intermediates which can be trapped and used preparatively. Some alkyl complexes which do not react thermally with unsaturated compounds, e.g. olefins, under the influence of UV light display high activity as polymerization catalysts.

1. Introduction**

The chemistry of alkyltransition-metal complexes is only thirty years old. Although *Frankland* reported dimethylzinc and diethylzinc[1] in 1849—compounds now regarded as milestones in organometallic chemistry—the following 100 years saw no further alkyl- or aryl-compounds of a single transition metal. Organotransition-metal compounds were thought to be "non-existing compounds", especially since calculations[2] suggested that the thermodynamically weak transition metal-carbon σ-bond was responsible for their instability. Despite this dim prognosis, *Piper* and *Wilkinson* succeeded, in 1955, in preparing Cp_2TiMe_2[3], a typical representative of this class of compounds: only two years later, the first homoleptic alkyltransition-metal compound followed with $TiMe_4$[4]. The spell thus broken, a vigorous development of the chemistry of alkyltransition-metal complexes set in. Of decisive importance was firstly the realization that the lability[5,6] of the transition metal-carbon σ-bond is generally of kinetic origin[7,8] and, secondly, experience demonstrating the ability of suitable ligands—such as carbon monoxide, cyclopentadienyl, phosphanes, phosphites, etc.—to stabilize the metal-carbon σ-bond. In the '70s, *Lappert*, *Wilkinson*, and *Schrock* succeeded in preparing thermally stable homoleptic alkyltransition-metal compounds: they employed alkyl ligands in which the favored decomposition pathways, e.g. β-hydrogen elimination, were blocked. Today, alkyl compounds of practically all transition metals are known and their chemistry has been reviewed in a series of articles[9-11].



Why are alkyltransition-metal complexes interesting? They are considered key intermediates in many industrially important catalytic processes: low-pressure polymerization of olefins in the Ziegler-Natta process, olefin isomerization, hydroformylation, ethylene oxidation in the Wacker-Hoechst process, and the Fischer-Tropsch hydrocarbon synthesis. Outside the laboratory or chemical plant, nature presents us with an important representative of this class of compounds, namely vitamin B_{12} (a protective factor against pernicious anemia). It contains a cobalt-carbon σ-bond and is of vital importance for both human and animal life.

Although the chemistry of organotransition-metal compounds began to flourish in the late '50s, photoinduced transformations of alkyltransition-metal compounds were relatively unknown until ten years ago. Only a few isolated studies had been carried out on alkylcobalt compounds in connection with coenzyme B_{12}[12-16] and a few observations on the titanium complex $TiCl_3Me$[17] and the norbornyl complexes M(1-norbornyl)$_4$ (M = Ti, Zr, Hf, V, Cr, Mn, Fe, Co)[18] were reported. Apart from this, the reaction of isopropyl Grignard reagents with transition-metal halides had been studied, and the alkyl complexes thus formed could be used preparatively as photolabile intermediates for the preparation of low-valent oligoolefin complexes[19-22]. This late interest in photoreactions is surprising, since the light-sensitivity of carbonyltransition-metal complexes had been discovered as early as 1891[23] and exploited extensively in the last 25 years[24-29]. In 1979, for the first time, a short summary of the then known results on the photochemistry of alkyltransition-metal compounds appeared[29]. The present article is a review of the ten year history of this rapidly expanding area.

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[**] Abbreviations used: Cp: η^5-cyclopentadienyl, Ind: η^5-indenyl, Flu: η^5-fluorenyl, Me: methyl, Et: ethyl, Pr: propyl, Bu: butyl, Pe: pentyl, Np: neopentyl, py: pyridine, bpy: bipyridine, phen: 1,10-phenanthrolene, Ar: aryl, CIDNP: chemically induced dynamic nuclear polarization experiments.

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2. Mechanism of Photoinduced Dealkylation

2.1. General Considerations

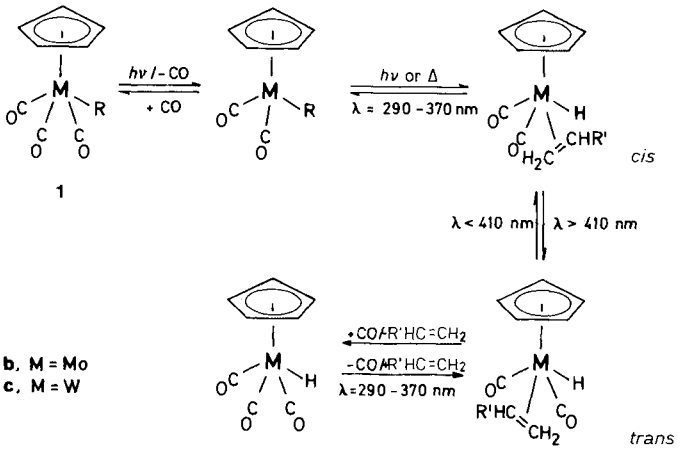
The bond energy of a transition metal-carbon σ-bond is comparable to that of a transition metal-carbonyl bond and varies between 100 and 300 kJ/mol; for structurally analogous compounds, its value depends on the position of the central metal in the periodic system, increasing in a given transition period from left to right and within a group on going from top to bottom, e.g. $Mn(CO)_5Me$: $D(Mn-Me) = 117$ kJ/mol; $Re(CO)_5Me$: $D(Re-Me) = 223$ kJ/mol[30]. Despite these relatively high dissociation energies, alkyltransition-metal compounds can decompose at low temperatures when the kinetic requirements are favorable. Their thermal stability can be markedly increased, however, when common decomposition pathways are blocked by suitable measures involving the alkyl ligand or the metal. Sometimes a high thermal stability may be coupled with an undesirably "braked" reactivity of the alkyl complex; in such cases, photochemical activation allows one to avoid harsh reaction conditions. A great advantage of the photochemical method is its independence of a fixed reaction temperature, thus allowing reactions to be conducted even at temperatures slightly above absolute zero.

The primary *physical* processes which occur immediately after photoexcitation, and which eventually cause the rupture of the metal-carbon σ-bond, are very complicated and are known only for a few, simple complexes. Depending on the complex type, a multitude of excited states must often be considered[29], i.e. the ligand internal excitation (LI), excitation of metal-centered d-electrons ("d-d" transitions; LF), metal-to-ligand charge-transfer excitations (MLCT), ligand-to-metal charge-transfer excitations (LMCT), or complex-to-solvent charge-transfer excitations (CSCT). These excited states often superimpose, are rarely separable, and, hence, occur together, especially when the photoexcitation is not conducted monochromatically.

Due to these problems, the photochemistry of alkyltransition-metal compounds is, as yet, the domain of the preparative chemist: identification of the primary *chemical* products from the photoreactions of model compounds allows conclusions to be drawn concerning the reaction mechanism. Matrix photolysis at 8–12 K has proven especially useful in this respect[31]. In the following discussion, the three most important mechanisms are briefly described: they may be—but are not necessarily—identical with the thermal decomposition mechanism.

2.2. Photoinduced Intramolecular β-Hydrogen Abstraction ("β-Elimination")

Intramolecular β-hydrogen abstraction can occur when the alkyl ligand has hydrogen atoms in the β-position with respect to the metal and the metal also has an empty coordination site. A well-studied example is the photoinduced dealkylation of the thermally stable complexes **1b**, **c** (R = Et, Pr, Bu[32,33], *n*Pe[34]); here, *all* the postulated intermediates could be characterized[33] (for reactions of **1a**, M = Cr, see Sections 2.3 and 3.3).



The first step consists of the reversible photoinduced dissociation of a carbonyl ligand, which produces an empty coordination site at the metal. In the subsequent β-hydrogen transfer to the metal, the newly formed olefin occupies this site, thus transforming the photolytically initially formed highly reactive 16-electron fragment $CpM(CO)_2R$ into a hydrido(olefin) complex with a noble gas configuration. During this transformation, the *cis*-isomer is formed, but rapidly converts into the thermodynamically more favorable *trans*-isomer. When the reaction is performed in pentane, the *trans*-isomer can be isolated and characterized and is surprisingly thermally stable.

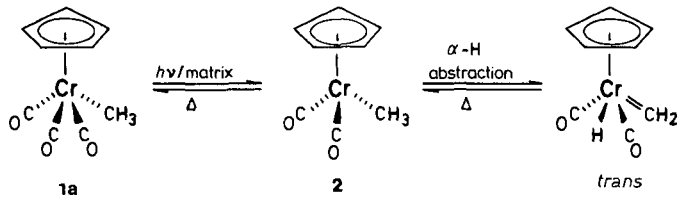
However, under photolysis conditions, the olefin ligand is easily replaced by carbon monoxide. The resulting hydrido complex $CpM(CO)_3H$ can be isolated from the reaction mixture, but either undergoes photolytic decomposition in the reaction solution[35,36] or reacts with unreacted starting material to give the corresponding alkane RH and the dimeric complex $[CpM(CO)_3]_2$. Photolyses in matrices at 12 K have shown that the various reactions in the scheme are reversible and that the concentrations of the intermediates can be influenced by the wavelength of the radiation used. In this fashion, the insertion of an olefin into the metal-hydrogen bond—a key reaction in hydroformylation—can be observed directly in a model system[37].

The complex $TiCl_3(Et)(Me_2PCH_2CH_2PMe_2)$[38] and the cation $[CpCo(Et)PR_3]^{\oplus}$ (R = *p*-tolyl)[39] are excellent candidates for β-elimination. Their molecular structures show a strong interaction between the metal and the hydrogen on the C_β atom; such agostic[*] ethyl groups can also be identified in the ^{1}H- and ^{13}C-NMR spectra.

2.3. Photoinduced α-Hydrogen Abstraction

Photoinduced α-hydrogen abstraction occurs under the same basic conditions as β-elimination; the difference is that the central metal can abstract hydrogen only from the α-position of an alkyl ligand. An example of such a reaction is the photolysis of the methyl compound **1a** (R = Me) leading to formation of a hydrido(methylene) complex[40].

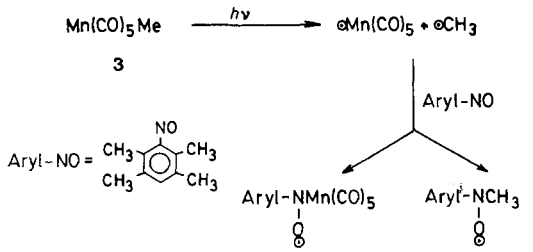
[*] The word agostic signifies a covalent interaction C–H–M in organotransition-metal compounds; M. Brookhart, M. L. H. Green, *J. Organomet. Chem. 250* (1983) 395.



An "α-abstraction" may also proceed intermolecularly, as was shown for CD_3TiCl_3[17]. If a complex fragment can undergo both α- and β-hydrogen elimination, the latter is favored almost exclusively. Due to their high reactivity, the (alkylidene)hydrido complexes formed in these photoinduced α-hydrogen abstractions can be detected only in matrices. In solution, the primary step is followed by undetermined subsequent reactions and, hence, the complete mechanism of the dealkylation remains open to speculation.

2.4. Photoinduced Cleavage of the Transition Metal-Carbon σ-Bond (Homolysis)

For the direct cleavage of a transition metal-carbon σ-bond, the required dissociation energy must be supplied by UV light. At first—similar to α- or β-elimination—the molecule absorbs light energy and is excited into one or several higher energy states[29]. The physical processes which occur at this stage proceed very quickly and are substantially more complicated than for organic molecules; they have, therefore, been elucidated unambiguously only in a few cases. Most frequently the photo-excitation is coupled with a charge transfer which causes the rupture of the metal-carbon bond. The initial products of this step are not stable; however, they may, in principle, be detected by suitable spectroscopic techniques (ESR and CIDNP) or indirectly, as in the photolysis of **3**, through trapping reactions[41].

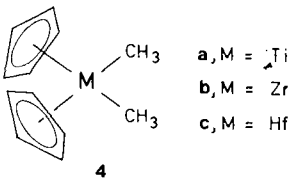


The alkyl radicals predominantly abstract hydrogen from other ligands or from the solvent; dimerization occurs only exceptionally.

3. Photoreactions of Alkyltransition-Metal Complexes

3.1. Photoreactions of Alkyl Complexes of Titanium, Zirconium, and Hafnium

The organometallic compounds of titanium, zirconium, and hafnium known up to 1973 are compiled in [42]; photoreactions of σ-organometallic complexes up to 1976 may be found in [43]. Among the known alkyl compounds containing metals of group IVB, results of photoreactions have been reported for the following: $TiCl_3Me$[17], M(1-norbornyl)$_4$ (M = Ti, Zr, Hf)[18], $M(CH_2Ph)_4$ (M = Ti, Zr)[44,45], Cp_2MMe_2 (M = Ti, Zr, Hf)[46-54], $(C_5H_4Me)_2MMe_2$ (M = Ti, Zr)[55], Ind_2MMe_2 (M = Ti, Zr, Hf)[67,68], Flu_2ZrMe_2[56], $Cp_2Ti(CH_2Ph)_2$[52], Cp_2MMeCl (M = Ti[53], Zr[57]), Cp_2ZrRX (R = CH_2Ph, CH_2SiMe_3, X = halogen)[57], Np_4Ti[58], and $Np_2ZrCl_2(PMe_3)_2$[59]. Photoreactions were first studied systematically for the complexes Cp_2MMe_2 (M = Ti, Zr, Hf) **4**[46,48].



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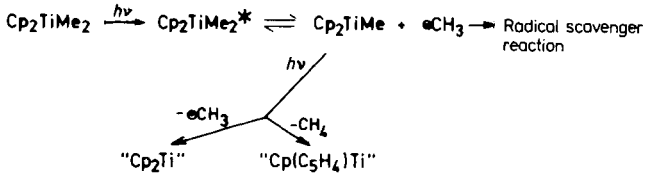
The complexes **4** can be completely dealkylated in solution by UV irradiation ($\lambda \geq 300$ nm); the gaseous product consists almost exclusively of methane (ca. 98%), with small amounts of ethylene and ethane. Photolysis reactions with partially deuterated **4a** in pentane show that the hydrogen required for methane formation—similar to the thermal decomposition[60-64] of the Cp_2MR_2 complexes (M = Ti, Zr, Hf; R = alkyl)—originates from the other methyl ligands as well as from the cyclopentadienyl ring, but not from the solvent. The mechanism of the hydrogen abstraction seems to be dependent both on the nature of the solvent and on the wavelength of the UV light employed: photolysis of **4a** in chloroform[50] leads to several chlorine-containing products and methane.

$$\underset{\mathbf{4a}}{Cp_2TiMe_2} \xrightarrow[-CH_4]{h\nu,\ CHCl_3} Cp_2TiMeCl,\ Cp_2TiCl_2,\ CpTiCl_3$$

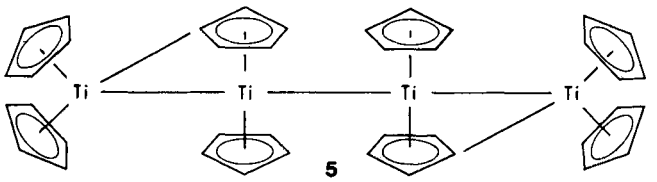
The production of $CpTiCl_3$ can be interpreted as evidence for the formation of cyclopentadienyl radicals during the photolysis, which, similar to methyl radicals, can be transferred to other substrates.

$$\underset{\mathbf{4a}}{Cp_2TiMe_2} + Mn_2(CO)_{10} \xrightarrow{h\nu} CpMn(CO)_3$$ [53]

In this dealkylation of **4a** the chloroform behaves in a manner which is known for other photoreactions in chlorinated solvents[65]. However, in the photoinduced decomposition of $Cp_2Ti(CD_3)_2$ with filtered UV light ($\lambda = 435.8$ nm) in deuterated solvents, only the cyclopentadienyl ligands suffer hydrogen abstraction—not other alkyl ligands[51]. ESR spectroscopic studies[52,53] of the photolysis of **4a** and Cp_2ZrR_2 (R = CH_2Ph, CH_2SiMe_3)[57] as well as radical trapping reactions with anthracene[47] indicate that alkyl radicals are generated during the irradiation. It can therefore be concluded that the primary step in the dealkylation is a photoinduced homolytic cleavage of the M–C σ-bond. CIDNP[55] experiments of the photolysis of $(C_5H_4Me)_2MMe_2$ (M = Ti, Zr) support this hypothesis and indicate that only very fast radical scavengers, such as nitrogen oxides, oxygen, or thiophenol, will be able to compete with the subsequent reactions:



The products of the dealkylation of **4** are gray to black, pyrophoric, and weakly paramagnetic. The best studied of these is "black titanocene" **5**, which is produced photochemically from **4a**. The thermal reaction of **5** with gaseous HCl at −78°C yields Cp_2TiCl_2 as the main product,



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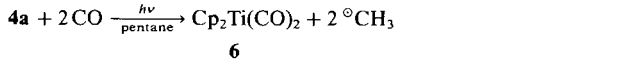
with small amounts of $CpTiCl_3$ and $(C_5H_4Cl)_3Ti_2Cl$. Excess bromine in benzene converts **5** into mainly $CpTiBr_3$ and Cp_2TiBr, accompanied by some $Cp(C_5H_4Br)_2TiBr$ and $Cp(C_5H_4Br)TiBr_2$. Carbon monoxide and **5** react in benzene in the dark to yield the monomeric dicarbonyl complex **6**, which has been characterized by X-ray structure determination[66].

During the photodealkylation of **4**, the cyclopentadienyl ligand is used as a hydrogen source, but when the photolysis is conducted in the presence of suitable ligands the metallocene skeleton remains intact. Thus, the photochemical reaction of **4a** with carbon monoxide in solution under normal conditions yields **6** within a few minutes.



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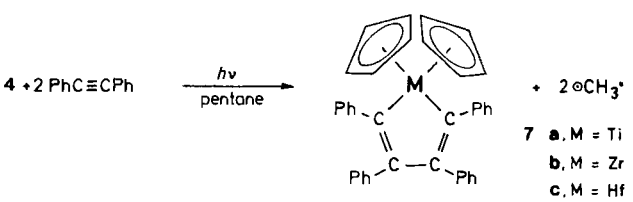
However, this method for the preparation of $Cp_2Ti(CO)_2$ fails with the Zr and Hf complexes **4b**, **c**, because these add carbon monoxide in the dark to form the acetyl complexes $Cp_2MMe(COMe)$ (M = Zr, Hf)[67,68]. The photocarbonylation demonstrates that transition-metal carbonyl complexes can not only be induced photochemically to lose CO[24-29], but may also be derived from suitable alkyl complexes with the aid of UV light. Upon UV irradiation, **4** reacts with diphenylacetylene **4** to afford the metallacycles **7**, whose identity was confirmed by X-ray structural determinations (Fig. 1)[69,70].



A 1:1 adduct is formed in the reaction of **4a** with C_2Ph_2[47,49], in which the alkyne apparently inserts into a Ti–C σ-bond to form exclusively the *cis*-isomer **8**.

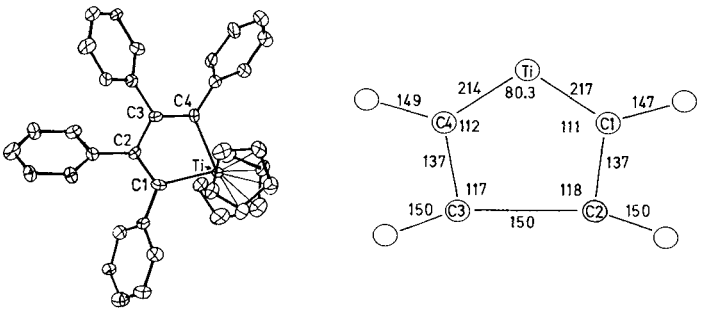
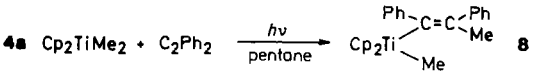


Fig. 1. Molecular structure of **7a** in the crystal (left); selected atomic distances [pm] and angles [°] (right).

Under the same reaction conditions, $C_2(C_6F_5)_2$ does not yield a titanacycle but only a *cis/trans*-mixture of a derivative analogous to **8**.



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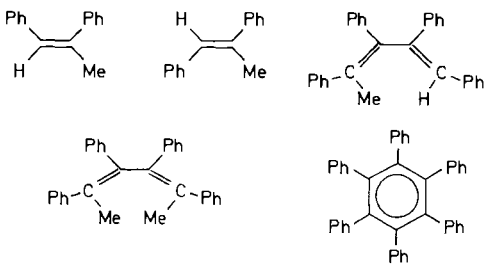
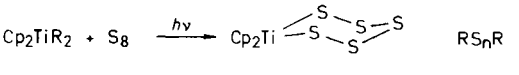
In the photoinduced reaction of **4a** with diphenylacetylene, much less methane is evolved than would be expected from the stoichiometry. During work-up of the reaction mixture, the following organic by-products which feature the former methyl ligands as substituents can be identified.



This mixture of products allows the conclusion to be made that either the free alkyne acts as a methyl trap or the Ti–C(Ph) σ-bond of **8** is ruptured homolytically. Subsequent uptake of hydrogen or dimerization of the radicals could then lead to the alkenes. Alkyne insertion into **7a** followed by elimination of the $(C_2Ph_2)_3$ moiety seems to be responsible for the formation of hexaphenylbenzene[71].

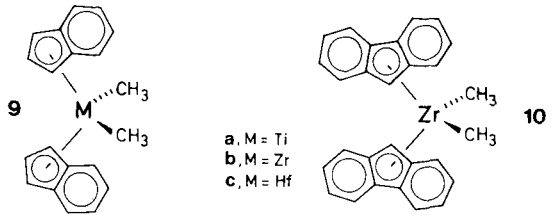
Another unusual reaction is the photochemical activation of elemental sulfur by **4a** or its phenyl derivative, which leads to Cp_2TiS_5 and other polysulfides[54]. With **4b** and **4c** this reaction does not occur.



R = Me, CH_2Ph

The indenyl complexes **9**[72,73], which are analogues of **4**, and the fluorenyl derivative **10** display similar reactivity to the parent cyclopentadienyl compounds[47]. Thus, pho-

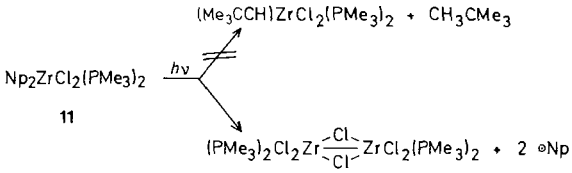
todealkylation results in almost exclusive formation of methane, with the aromatic five-membered ring serving as hydrogen source. The determination of the structures of the



metal-containing, pyrophoric photolysis products is complicated by their nonvolatility and insufficient solubility in noncoordinating solvents, which suggests the formation of polynuclear bisindenyl- or bisfluorenyl-complexes.

By analogy to **4a**, photochemical reaction of **9a** with carbon monoxide converts it into the corresponding dicarbonylbis(indenyl)titanium, $Ind_2Ti(CO)_2$[48].

An attempt to transform $Np_2ZrCl_2(PMe_3)_2$ **11** into the corresponding neopentylidene complex by photoinduced α-hydrogen abstraction failed[59].



It is assumed that homolysis of both Zr–C σ-bonds leads to a chlorine-bridged binuclear complex. The course of the reaction presumably reflects the fact that the electron deficiency on the central metal is not sufficiently large to activate the alkyl ligand to α-elimination.

In the dark, the alkyl complexes $M(CH_2Ph)_4$ (M = Ti, Zr)[44,45] and Np_4Ti[58] catalyze the polymerization of methyl methacrylate, styrene, or other olefins either slowly or not at all; however, upon irradiation with UV light they develop considerable catalytic activity. Ti^{III} or Zr^{III} species as well as alkyl radicals have been proposed as the initiators or catalysts for the onset of polymerization.

3.2. Photoreactions of Alkyl Complexes of Vanadium, Niobium, and Tantalum

Reports of photoreactions involving alkyl complexes of the metals of group VB are very sparse. The main reason could be that thermal reactions have opened up such an extensive chemistry as to make the photochemical variant seem unnecessary. In the last ten years, especially *Schrock* has elegantly shown how thermally induced α-eliminations can transform alkyl complexes into alkylidene and alkylidyne compounds[10,74]. The few photoreactions reported offer an alternative to the thermal reactions, inasmuch as they proceed faster and sometimes more selectively. Thus, the two-electron ligand C_2H_4 in complex **12** cannot be exchanged thermally for phosphane. The reaction[75]

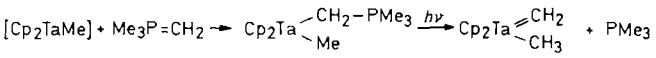
$$Cp_2Ta(C_2H_4)Me + PMe_3 \xrightarrow[C_6D_6]{h\nu} Cp_2Ta(PMe_3)Me + C_2H_4$$

12

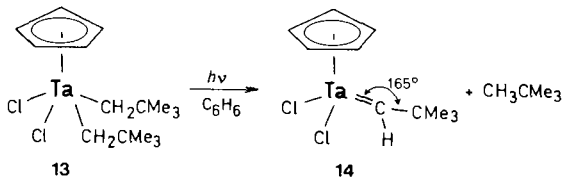
proceeds only photochemically and is initiated by the photoinduced loss of the olefin; the 16-electron fragment Cp_2TaMe then adds phosphane. Similarly, the reaction[75]

$$\mathbf{12} + Me_3P{=}CH_2 \xrightarrow{h\nu} Cp_2Ta(CH_2)Me + PMe_3 + C_2H_4$$

only proceeds under the influence of UV light, and the intermediate [Cp_2TaMe] again plays a key role. The decomposition of $Me_3P{=}CH_2$ is thus photochemically induced by **12**.



α-Hydrogen elimination in the dineopentyl complex **13** is accelerated by UV light[76,77].



13 **14**

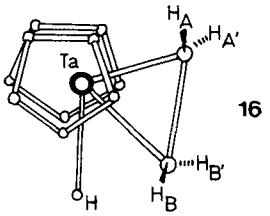
The difference with respect to the thermal reaction consists in the formation of considerable amounts of 2,2,5,5-tetramethylhexane, probably from photolytically generated neopentyl radicals. The driving force for these eliminations, i.e. the tendency of the metals to abstract hydrogen, seems to be strongly correlated with the electron deficiency of the metal (14-electron complex, formal oxidation state of Ta: +5).

The photolyses of the 16-electron complex Cp_2VMe and the 17-electron compounds Cp_2MMe_2 **15** (**a**, M = V; **b**, M = Nb; **c**, M = Ta) have also been reported[78,79]. Irradiation of **15**b, **c** in hydrocarbons yields methane as the main gaseous product (99%), mixed with traces of ethylene and ethane. Only the photoinduced decomposition of **15a** yields a methane/ethane mixture (2 : 1). It is assumed that this photoreaction proceeds analogously to that of complexes **4** via homolytic cleavage of the M–CH_3 bond. Reactions with partially deuterated starting materials demonstrate that the methyl ligands, the cyclopentadienyl rings, and the solvent serve as the hydrogen reservoir. These results differ from the thermal decomposition of **15a**, **b**[80,81], which yields only methane, and from the photolysis of **4a**, in which the methyl radicals do not abstract hydrogen from the solvent. The metal-containing photolysis products are not the well-known metallocenes of the metals of group VB, but rather nonvolatile, probably polynuclear complexes which could arise analogously to "black titanocene" **5**.

An exception is the photolysis of **15c** in pentane, during which Cp_2TaMe_3 could be detected—apparently produced by photoinduced alkyl-transfer.

$$Cp_2TaMe_2 \xrightarrow{h\nu} Cp_2TaMe + {}^{\ominus}CH_3 \xrightarrow{+\,15c} Cp_2TaMe_3 + \tfrac{1}{x}(Cp_2Ta)_x$$
15c

Remarkable is the photolysis of $Cp_2Ta(CO)Et$[82] in solution which leads to $Cp_2Ta(C_2H_4)H$ **16** via CO-loss and subsequent β-hydrogen elimination.



16

The spectroscopic characterization of the product indicates a metallacyclopropane complex in which the C–C axis lies in the plane of symmetry of the molecule.

3.3. Photoreactions of Alkyl Complexes of Chromium, Molybdenum, and Tungsten

The photochemistry of alkyl complexes of group VIB metals is easily reviewed: the most intensively studied photoinduced reactions by far are those of the cyclopentadienyl compounds $CpM(CO)_3R$ **1** (**a**, M = Cr; **b**, M = Mo; **c**, M = W; R = alkyl) and of a few analogous indenyl complexes. These reactions are characterized by the substitution of carbonyl ligands, while the alkyl ligand either maintains its terminal position or rearranges intramolecularly. To date, the photoinduced reactions of the two homoleptic alkyl compounds WMe_6[83] and $CrNp_4$ **17**[84], of the metallacyclobutane derivatives $Cp_2W(CHRCHRCH_2)$ (R = H, Me)[85], and of the cation in $[Cp_2WMe_2][PF_6]$ **19**[86] have only been reported briefly.

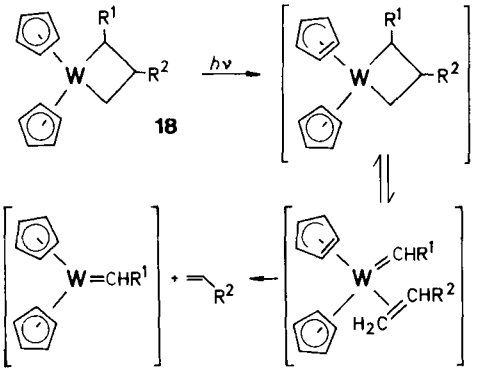
Instead of the desired complex "$W(CH_2)_3$", the thermal and photochemical "decomposition" of $WMe_6 \cdot PMe_3$ in trimethylphosphane led to isolation of *trans*-$Me_2W(PMe_3)_4$, which was characterized by X-ray structure analysis[83]. The four methyl ligands released form methane. No statement is made about the reaction mechanism.

Photolysis of $CrNp_4$ **17** in hexane or toluene yields neopentane, 2,2,5,5-tetramethylhexane, elemental chromium, and a black pyrophoric residue[84]. During the irradiation, unsaturated compounds such as styrene, methyl acrylate, methyl methacrylate, vinyl acetate, and ethylene can be polymerized under mild conditions; in the presence of carbon monoxide, $Cr(CO)_6$ is formed. These results indicate that the photolysis of **17** involves stepwise scission of chromium-carbon σ-bonds until the chromium finally reaches the oxidation state zero. Alkyl radicals are probably responsible for the initiation of polymerization.

$$Cr^{IV}Np_4 \xrightarrow{h\nu} Cr^{IV}Np_4^{*} \xrightarrow[-\odot Np]{} Cr^{III}Np_3$$
17

$$\xrightarrow[-\odot Np]{h\nu} Cr^{II}Np_2 \xrightarrow[-\odot Np]{h\nu} \cdots Cr^{0}$$

The metallacycle **18** decomposes thermally (80 °C) to afford a mixture of cyclopropane and propene ($R^1 = R^2 = H$) or 1-butene ($R^1 = Me$, $R^2 = H$) or isobutene ($R^1 = H$, $R^2 = Me$). In contrast, photochemical decomposition of **18** generates ethylene and some methane ($R^1 = R^2 = H$)[85]. The first step in the reaction is the change from η^5- to η^3-coordination of a cyclopentadienyl ligand ("ring slippage") followed by the breaking of the metallacyclobutane ring—as one step in the metathesis mechanism. However, none of the postulated intermediates could be isolated.



Photolysis of **19** in the presence of L (L = pyridine, acetonitrile, dimethylphenylphosphane) leads to **20**–**22**[86].

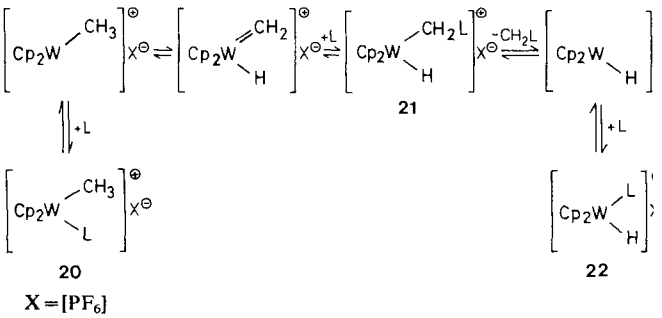
$$[Cp_2WMe_2]^{\oplus}X^{\ominus} \xrightarrow{h\nu,\,L} [Cp_2WMe(L)]^{\oplus}X^{\ominus}$$
19 **20** L = py, MeCN, PMe_2Ph

$$\mathbf{19} \xrightarrow{h\nu,\,L} [Cp_2WH(CH_2L)]^{\oplus}X^{\ominus}$$
21 L = PMe_2Ph

$$\mathbf{19} \xrightarrow{h\nu,\,L} [Cp_2WH(L)]^{\oplus}X^{\ominus}$$
22 L = py, MeCN

X = $[PF_6]$

The thermal reaction yields a completely different product mixture; MeCN does not react with **19** at all. The reaction is apparently initiated by homolytic dissociation of an alkyl ligand and—analogous to the thermal decomposition of $[Cp_2WMe(PR_3)][PF_6]$[87,88]—subsequent α-hydrogen elimination.



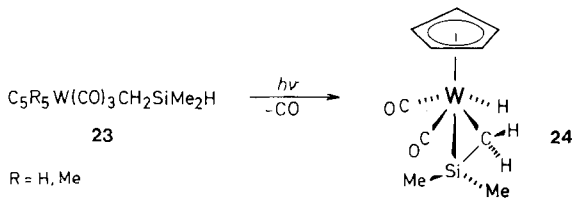
X = $[PF_6]$

The first step in this mechanism differs from that in the photolysis of **18**. No prediction can therefore be made, a priori, about the way in which the metal creates the empty coordination site required for the α- or β-hydrogen elimination.

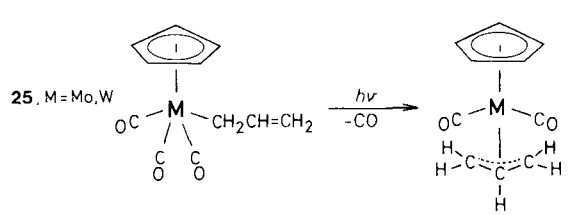
$CpM(CO)_3R$ complexes **1** (R = alkyl) have been of interest for some time, because the CO ligands can readily be substituted thermally or photochemically:

$$CpM(CO)_3R \xrightarrow[L]{h\nu \text{ or } \Delta} CpM(CO)_2(L)R + CO$$
1 and/or $CpM(CO)(L)_2R + 2CO$
and/or $CpM(CO)_2(L)COR$
L = n-donor

The resulting mono- and disubstitution products are well suited for IR- and NMR-spectroscopic studies, so that these complexes allow kinetic studies to be made on *cis/trans*-isomerizations. The mechanism of the substitution is well-known from the photochemistry of carbonyltransition-metal complexes[24–29]: in the first and rate-determining step a carbonyl ligand is lost, and the coordinatively unsaturated complex fragment $CpM(CO)_2R$ stabilizes itself by addition of a new ligand L. On the basis of photoelectron spectra[89] and X-ray structural studies[90], it is expected that in the compounds **1** not only the metal-carbonyl bond but also the metal-carbon σ-bond is subject to cleavage by UV light. Such a simultaneous cleavage is, for example, observed in the photolysis of $Mn(CO)_5Me$ **3**[41]. Photolysis of **1** in noncoordinating solvents indeed results in dealkylation and formation of $[CpM(CO)_3]_2$ as the major product. It is therefore tempting to assume a photoinduced homolysis of the metal-carbon σ-bond as the key reaction in the dealkylation. In reality, the mechanism seems to vary according to the type of alkyl ligand. The course of the photolysis of **1b, c** can be described completely when the alkyl ligand has hydrogen in the β-position[32–35] (cf. Section 2.2). This enables a photoinduced, intramolecular, β-hydrogen elimination which can be used preparatively to obtain olefin hydride complexes of the type *trans*-$CpM(CO)_2$(olefin)H or hydrides of the composition $CpM(CO)_3H$. Also interesting is the photolysis of **23**, which proceeds via β-hydrogen elimination and formation of the three-membered metallacycle **24**[91].

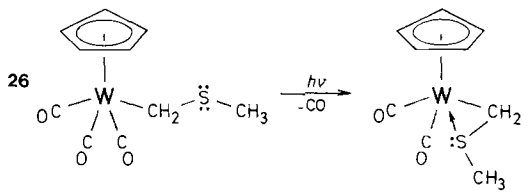


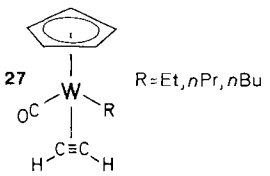
If the alkyl ligand in **1** contains a potential donor function, e.g. in the form of a double bond or a lone pair of electrons, the 16-electron fragment can stabilize itself without a hydrogen migration. Such $\sigma \rightarrow \pi$-rearrangements have long been known for $CpM(CO)_3(\eta^1$-allyl) complexes such as **25**[92–94] and also for the benzyl derivatives $CpM(CO)_3CH_2Ph$[33,95–98] (M = Mo, W).



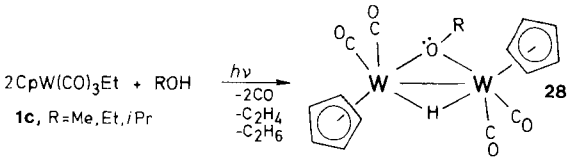
Similarly, upon UV irradiation **26** stabilizes itself via a lone pair of electrons on sulfur[99].

If the photolysis of $CpM(CO)_3R$ **1b,c** (M = Mo, W; R = Et, Pr, etc.) is conducted in the presence of potential ligands L, β-hydrogen elimination competes with the CO substitution. In the photoinduced reaction of **1b,c** (R = Et) with PMe_3 in pentane, not only the substitution product $CpM(CO)_2(PMe_3)Et$ but also $CpM(CO)_2(PMe_3)H$, $CpM(CO)_3H$, and ethene are detected[100]. Acetylenes serve as ligands: in the photoinduced reaction with **1c**, the complexes **27**[101] are formed, which are relatively resistant towards photoinduced β-hydrogen migration.





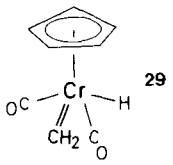
This behavior is an important indication of the presence of a four-electron alkyne ligand in **27**[101].



A β-hydrogen elimination is also the basis for the photoinduced reaction of **1** ($R \neq Me$) with alcohols, which leads to formation of alkoxo- and hydrido-bridged binuclear complexes **28**.

28 is also accessible via photoinduced reaction of $CpW(CO)_3H$ or $CpW(CO)_2$(olefin)H with alcohols. Thus, it can be assumed that the hydrido complexes are the true active species. Consequently, irradiation of the methyl derivative $CpW(CO)_3Me$ in the presence of alcohols does not yield **28**.

UV irradiation of the methyl derivatives of **1** also results in dealkylation and formation of the binuclear complexes $[CpM(CO)_3]_2$. The gas formed consists only of methane. Experiments with deuterium labeled starting materials show that the hydrogen required for the methane formation is mostly abstracted from the cyclopentadienyl ring[105]. The mechanism of the dealkylation appears to be very complicated and dependent on the solvent. As established by photolyses in gas matrices[106], polymer films[107,108], and in solution[98,104], the first step in all cases is a photoinduced dissociation of a carbonyl ligand. The resulting 16-electron fragment can then undergo a reversible α-elimination (cf. Section 2.3), as shown for the fragments $CpCr(CO)_2Me$[40] and $CpMo(CO)_2CF_3$[109]. The highly reactive species **29** then decomposes further via a reaction of undetermined mechanism in which binuclear methylene-bridged hydrido complexes could play a role.



29

However, the $CpM(CO)_2Me$ fragment can also undergo a photoinduced homolysis of the metal-carbon σ-bond[107, 108, 110].

$$CpM(CO)_3CH_3 \xrightarrow[\text{solvent}]{h\nu} CpM(CO)_3CH_3^*$$

1 (R = Me)

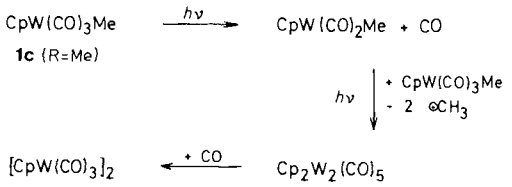
$$CpM(CO)_3CH_3^* \rightleftharpoons [CpM(CO)_2CH_3] + CO$$

$$[CpM(CO)_2CH_3] \xrightarrow{h\nu} [CpM(CO)_2]^{\odot} + {}^{\odot}CH_3$$

$$[CpM(CO)_2]^{\odot} \underset{-CO}{\overset{+CO}{\rightleftharpoons}} [CpM(CO)_3]^{\odot}$$

$$2[CpM(CO)_3]^{\odot} \rightleftharpoons [CpM(CO)_3]_2$$

An alternative mechanism for the photoinduced decomposition of **1c** (R = Me) is discussed in which methyl radicals abstract hydrogen from the solvent.



For such a mechanism one would expect dimerization of methyl radicals, leading to formation of ethane; however, this is not observed[110].

The influence of the solvent on the photolysis of **1** is especially marked for chloroform[98, 105, 111]: irrespective of the alkyl ligand, **1b** and **c** are transformed into $CpM(CO)_3Cl$, whereas **1a** suffers complete decarbonylation to give $[CpCrCl_2]_2$. $CpCr(CO)_3Cl$, which is unknown to date, could not be detected.

Besides coordinating solvents, ligands can trap the fragment $CpM(CO)_2R$ which results from the photolysis of **1** (R = Me), thereby producing the monosubstituted compounds $CpM(CO)_2(L)R$ (L = phosphane, phosphite, olefin). The thermal reaction also leads to substitution, but a CO-insertion or alkyl migration occurs simultaneously to produce an acyl ligand[100, 112].

$$CpM(CO)_3Me + L \xrightarrow[-CO]{h\nu} CpM(CO)_2(L)Me$$

1 (R = Me) *cis/trans* **30**

M = Mo, W; L = PPh_3[112]
M = Cr, Mo, W; L = $P(OMe)_3$, $P(OPh)_3$, PPh_3[103, 113–115]
M = Cr, Mo, W; L = PMe_3[116, 117]
M = W; L = C_2H_4[118, 119]

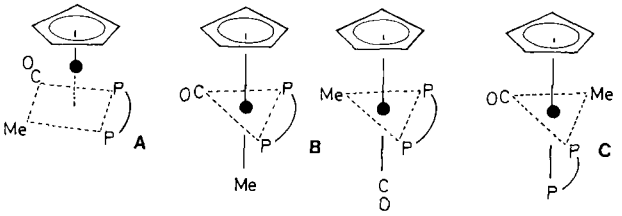
Some monosubstitution products **30** can undergo further CO substitution, generating the complexes **31**.

$$CpM(CO)_2(L)Me + L \xrightarrow[-CO]{h\nu} CpM(CO)(L)_2Me$$

cis/trans **31**

M = Cr, W; L = $P(OMe)_3$[103]
M = Cr, Mo, W; L = PMe_3[116]

Bidentate phosphanes can also be employed in this reaction and yield the isomers **A**, **B**, and **C**[120].



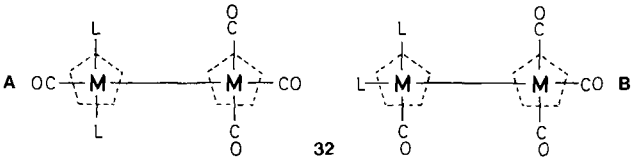
The analogous indenyl(methyl) complexes behave similarly to **1**[116]. In contrast to the cyclopentadienyl complexes, which always retain the cyclopentadienyl ring tightly bound, the photoinduced reaction of the indenyl complexes with trimethylphosphane results in loss of both the indenyl and methyl ligands. The reaction rate decreases along the series Cr ≫ Mo > W.

$$IndM(CO)_3Me + 4\,PMe_3 \xrightarrow[-CO]{h\nu} cis\text{-}M(CO)_2(PMe_3)_4 + {}^{\odot}CH_3 + {}^{\odot}Ind$$

The PMe_3-disubstitution products **31** and the corresponding indenyl derivatives are Lewis bases, because both the alkyl ligand and the PMe_3 ligands strongly increase the electron density at the metal. The alkyl ligand in these complexes can be exchanged cleanly for a chloride ligand:

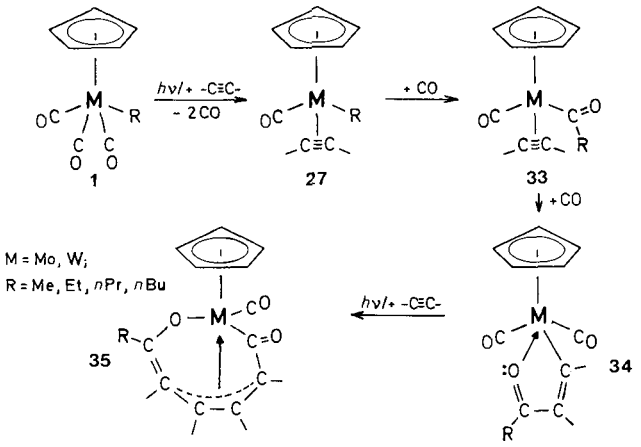
$$CpM(CO)(PMe_3)_2Me \xrightarrow[-{}^{\odot}CH_3]{CHCl_3/\text{silica gel}} CpM(CO)(PMe_3)_2Cl$$

The Lewis base character seems also to be the reason for the formation of the binuclear complexes **32** in the photoinduced reactions of **1** with L = PMe_3[116] (isomers **A** and/or **B**).

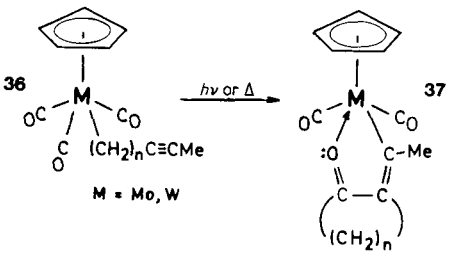


The photoinduced reactions of **1b**, **c** (R = Me) with alkynes are best studied with the tungsten complex, since the products are thermodynamically and kinetically more stable than those of the molybdenum complexes.

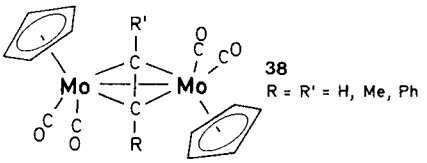
All intermediates in this reaction series, whose first and last steps require UV light, can be isolated and characterized for M = W[121–124] and used in a multitude of further reactions. For M = Mo, only the complexes **34**[122–126] and **35**[124, 126] can be detected. Analogous derivatives can be obtained from the indenyl complex $IndM(CO)_3Me$ (M = Mo, W)[127], the trifluoromethyl compound



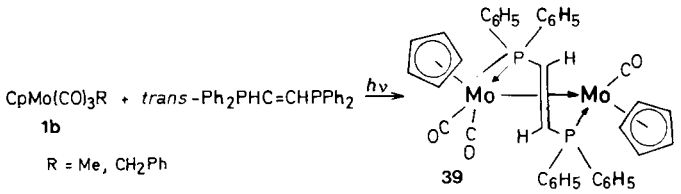
$CpMo(CO)_3CF_3$[128], and the η^1-allyl complex $CpMo(CO)_3(\eta^1\text{-}C_3H_5)$ **25** (M = Mo)[129]. Similarly, the thermal or photochemical rearrangement of **36** leads to **37**[130].



In contrast to this reaction scheme, the molybdenum complex **1b** forms binuclear complexes **38**[104] in low yields; these may also be generated by allowing $[CpM(CO)_2]_2$ (M = Cr, Mo, W) to react with alkynes[131-140] in the dark. In the photoinduced reaction with alkynes, **1b**

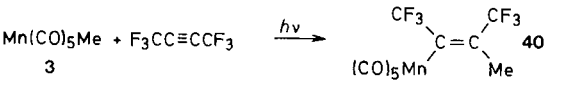


is apparently subject to a competition between dealkylation and a partial decarbonylation, which leads via $[CpMo(CO)_2]_2$ to complex **38**. A similar explanation also seems plausible for the formation of **39**[141].

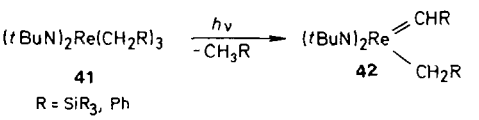


3.4. Photoreactions of Alkyl Complexes of Manganese and Rhenium

Only very few examples of photoreactions of alkyl compounds of manganese and rhenium are known. Of importance is the complex $Mn(CO)_5Me$ **3**, in which both the manganese-carbon σ-bond and the manganese-carbonyl bond can be cleaved homolytically[41] (Section 2.4). The insertion of alkynes into the Mn–C σ-bond of **3**[142], forming the complexes **40**, often proceeds only with the help of UV light[129].



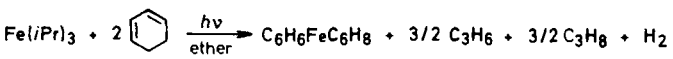
α-Hydrogen elimination in some alkyl(imido) complexes proceeds only photochemically (**41** → **42**)[143,144]; however, this method fails to convert **41** into the methyl(methylene) complex $(t\text{BuN})_2Re(CH_2)Me$.



$Cp_2Re(alkyl)$ compounds[145] are surprisingly stable to UV radiation: the mass spectrum of Cp_2ReEt certainly shows the fragment $Cp_2ReH^{\oplus}$, which indicates β-hydrogen elimination; however, it was not possible to thermally or photochemically dealkylate $Cp_2Re(alkyl)$ complexes.

3.5. Photoreactions of Alkyl Complexes of Iron, Ruthenium, and Osmium

The first photoinduced reactions of alkyl complexes of iron, ruthenium, and osmium date back to 1962, when the light sensitivity of the unisolated isopropyl complexes $M(i\text{Pr})_3$ (M = Fe, Ru, Os) was exploited for the preparation of olefin complexes in which the metal was formally in the oxidation state zero[19-21].

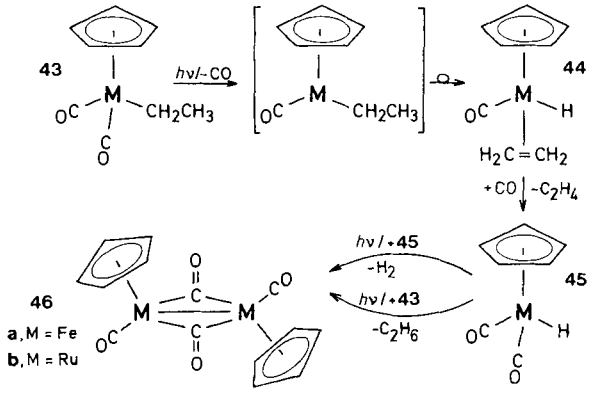


Although the individual reaction steps were not elucidated in any detail, the formation of propene points to a β-hydrogen elimination and the intermediate formation of $Fe(i\text{Pr})_2(C_3H_6)H$. The loosely bound propene ligand could be displaced by free olefin C_6H_8, which then supplies the hydrogen for the two propyl leaving groups. Complexation of a further C_6H_8 molecule leads finally to $C_6H_6FeC_6H_8$.

The photochemistry of $CpM(CO)_2R$ complexes (M = Fe, Ru; R = Me, Et)[146-148] has been studied extensively. The mechanism of photodealkylation resembles that of the complexes **1**: thus, photolysis of **43a, b** certainly proceeds via a β-hydrogen elimination.

Only **44b** can be stabilized and identified in a matrix[147,148]. In contrast, the hydrido(olefin) compounds $CpRu(PPh_3)(olefin)H$, which are thermally accessible from $CpRu(PPh_3)_2R$ complexes, exhibit considerably higher kinetic and thermal stability[149,150].

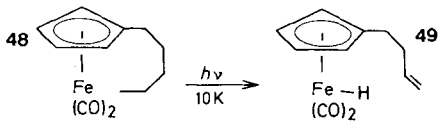
In the photolysis of **43b** in solution, the hydrido-bridged binuclear complex $[CpRu(CO)H]_2$ can be detected[148], which can be interpreted as a product of the photolysis of **45b**.



The methyl compounds **47** are easily dealkylated in solution; apart from a little carbon monoxide, only methane can be detected in the reaction gas.

$CpM(CO)_2Me$
47, **a**, M = Fe; **b**, M = Ru

The nearly quantitative formation of **46** arises because the cyclopentadienyl ring, the methyl ligands of other molecules, and the solvent serve as sources of hydrogen. Only traces (ca. 2%) of free radicals seem to be involved[146]. In the photolysis of **47a** in a carbon monoxide matrix at 12 K, $(\eta^3\text{-Cp})Fe(CO)_3Me$ can be identified[151]. Further support for such a "ring slippage" mechanism—which opens up a free coordination site at the metal—comes from the matrix photolysis of **48**, which leads to **49**[152].



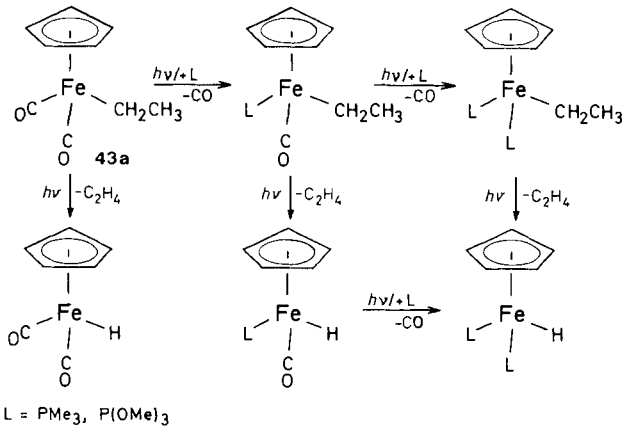
On the other hand, the photolyses of $CpFe(CO)_2(\eta^1\text{-}C_3H_5)$ **50**[93] and its η^1-1-(2,2-difluoro-1-trifluoromethylvinyl)-3,3,3-trifluoro-2-trifluoromethyl-1-propenyl derivative[153] generate the corresponding η^3-allyl complexes via CO-dissociation.

$$CpFe(CO)_2(\eta^1\text{-}C_3H_5) \xrightarrow[-CO]{h\nu} CpFe(CO)(\eta^3\text{-}C_3H_5)$$
50 **51**

Extensive studies have been undertaken on the photoinduced reaction of complexes **47a** and $(\eta^5\text{-}C_5H_3R'R'')Fe(CO)_2Me$ (R′ = R″ = alkyl) with phosphanes and phosphites L[154–166]. By analogy with the reactions of **1**, mono- and disubstitution products are formed; in contrast to the thermal reaction, however, the alkyl ligand maintains its terminal position. In this context, the ethene complexes $CpM(CO)(C_2H_4)Me$ (M = Fe, Ru)[148] should be mentioned, since they represent the only known alkyl complexes of this type.

If alkyl ligands with β-hydrogen are used, CO-ejection followed by β-hydrogen elimination can be observed, which proceeds with loss of the olefin ligand to afford the corresponding hydrido derivatives.

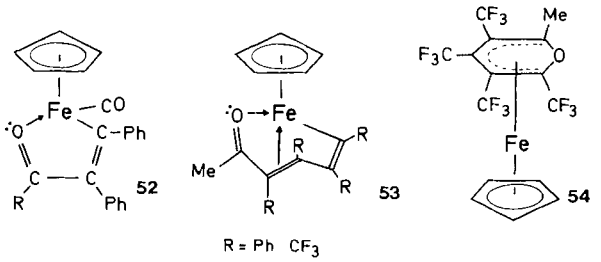
This subsequent reaction may be suppressed when a large excess of ligand is employed in the substitution reaction.



L = PMe_3, $P(OMe)_3$

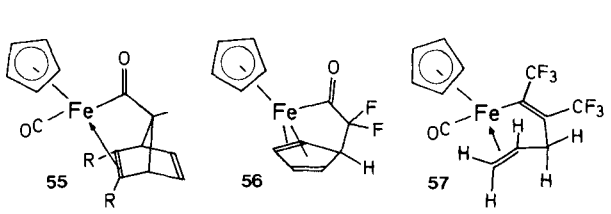
The photoinduced reaction of **43a** with ethene in pentane solution[148] is unusual: loss of the alkyl and one of the carbonyl ligands leads to the binuclear complex $[CpFe(CO)(C_2H_4)]_2$, which exhibits dynamic behavior similar to dimeric **46a**[167]. The analogous ruthenium compound **43b** does not undergo this reaction.

The $CpFe(CO)_2R$ complexes also react with alkynes: irradiation of a solution of **47a** and diphenylethyne yields a 1:1-adduct **52**, which is transformed into the seven-membered metallacycle **53** (R = Ph) via photoinduced alkyne insertion[146]. This type of complex ($R = CF_3$) together with **54** is also obtained in the reaction with hexafluoro-2-butyne[129]. Similar metallacycles are formed in the thermal reaction of $CpRu(PPh_3)_2H$ with alkynes[168].



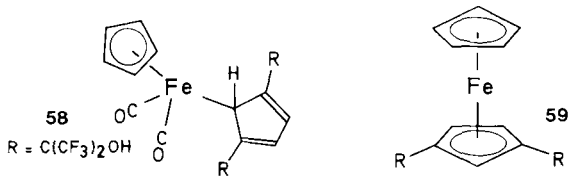
R = Ph CF_3

In the thermal reaction, however, only 1,2,3,4-tetraphenylferrocene can be detected[169]. A ruthenium complex $CpRu(PPh_3)(PhC{=}CMe{-}COMe)$ analogous to **52** is thermally accessible from $CpRu(PPh_3)_2Me$ and $PhC{\equiv}CCOMe$[170]. More complicated metallacyclic complexes of the type **55** ($R = CF_3$) and **56** are obtained in the

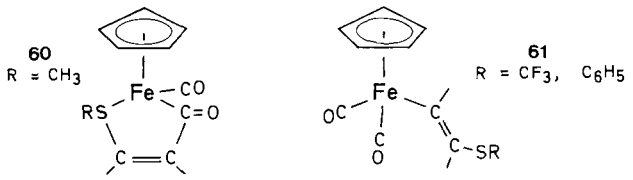


photoinduced reaction of $CpFe(CO)_2(\eta^1\text{-}C_5H_5)$ with $F_3CC{\equiv}CCF_3$ or C_2F_4[129]; the reaction of **50** and $F_3CC{\equiv}CCF_3$ leads to **57**. The photoinduced rearrange-

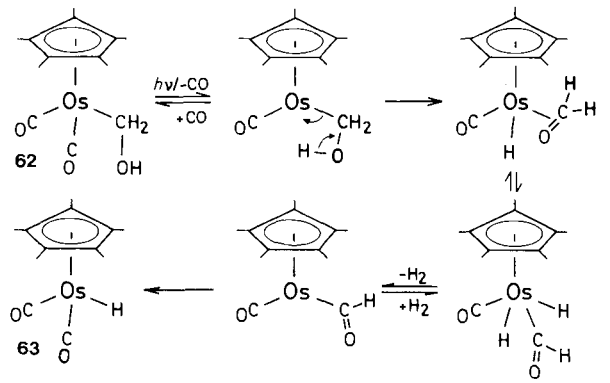
ment of the alkyl compound **58** yields the ferrocene derivative **59**[129], which can also be prepared thermally from ferrocene and hexafluoroacetone[171].



Completely different results are obtained from the reactions of alkynes with alkylthiolate complexes of the type $CpFe(CO)_2SR$: depending on whether R is electron-donating or electron-withdrawing, metallacyclic complexes **60**[172,173] or the insertion products **61**[174] are formed.



Remarkable is a retro-Fischer-Tropsch step which occurs in the photolysis of **62**, generating $C_5Me_5Os(CO)_2H$ **63**, CO, and H_2[175]. Based on studies with partially deuterated starting materials, a mechanism is proposed which involves abstraction of hydrogen from the β-position.

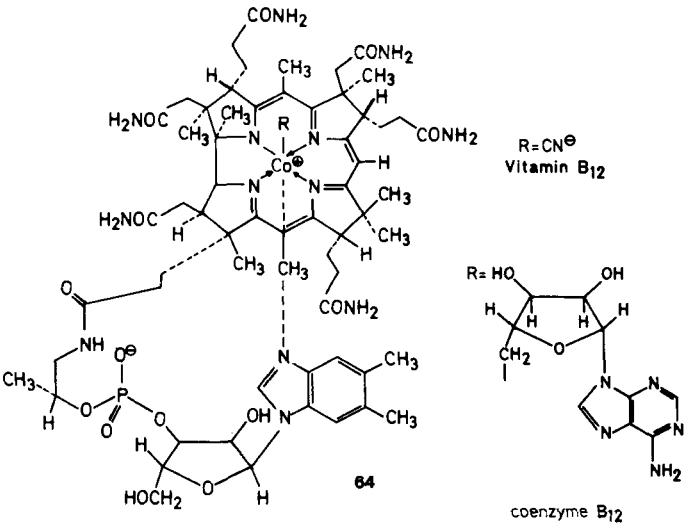


The metal-carbon σ-bonds of methylene bridges in polynuclear complexes prove to be very stable photochemically: thus, UV irradiation of $Cp_2Ru_2(CO)_4(\mu\text{-}CH_2)$ **63**[176] only results in loss of a CO to yield $Cp_2Ru_2(CO)_3(\mu\text{-}CH_2)$: the CH_2-bridge remains intact.

3.6. Photoreactions of Alkyl Complexes of Cobalt

All cobalt(III)-alkyl complexes are light sensitive, and the photochemical studies of this class of compounds are extensive. The most thorough studies have been carried out on vitamin B_{12} **64** and a series of simpler derivatives.

Vitamin B_{12} and "coenzyme B_{12}" contain a corrin ring system with a cobalt atom in the center. The central metal is formally in the oxidation state +3 and is axially coordinated by a base (5,6-dimethylbenzimidazole) and a cyanide



or 5′-deoxyadenosyl ligand. In order to obtain a "spectroscopic handle" on this complicated molecule, a multitude of simpler model compounds has been synthesized which exhibit the characteristic features of the parent molecule: thus, the cyanide ligand can be replaced by the methyl group (cobalamin), the corrin ring system can be substituted by other macrocyclic chelating ligands or the simple dimethylglyoxime, and the complicated base 5,6-dimethylbenzimidazole can be replaced with simple nitrogen bases such as pyridine. In the following discussion, all these species are abbreviated [Co]R.

Photoreactions of [Co]R compounds are covered extensively in [28,177–180], and hence only a brief recapitulation will be presented here: The alkylcobalamins show absorption bands of weak to medium intensity ($\varepsilon = 1000$—3000) in the range 350 to 470 nm. These bands are due to electronic transitions between axial orbitals. Upon irradiation with visible light, antibonding axial MOs are occupied[181]. The resulting photo-induced charge-transfer leads to cleavage of the relatively weak cobalt-carbon bond ($D = 85$—125 kJ/mol[182]). The photochemically induced dissociation is considered the rate-determining step in nearly all photolyses of cobalt-σ-organyl compounds.

$$[Co^{III}]R \overset{h\nu}{\rightleftharpoons} \{[Co^{II}] + {}^{\odot}R\}$$

The cobalt(II)-species and the alkyl radical coexist initially as a caged radical pair and can be detected by ESR spectroscopy[183–185] and flash photolysis[186]. If the lifetime of the alkyl radicals is sufficiently long, they can dimerize[187], disproportionate, or abstract hydrogen from other ligands or from the solvent. Alkyl compounds with β-hydrogen are preferentially dealkylated by this mechanism, but can also suffer β-hydrogen elimination[188]. The resulting reduced form of the cobalamin is known as B_{12r}.

Alkylcobaloximes and alkylcobalamins with electron-withdrawing substituents on the alkyl ligand deviate from this reaction scheme: photolysis of formylmethylcobaloxime or -cobalamin results in formation of acetaldehyde and cobalt(III) complexes[189].

$$[Co^{III}]-CH_2CHO \xrightarrow{h\nu} \{[Co^{II}] + {}^{\circ}CH_2CHO\}$$
$$\downarrow -[Co^{III}]$$
$$CH_3CHO \xleftarrow{+H^{\oplus}} {}^{\circ}CH_2CHO$$

Co^{II} intermediates cannot be detected in this reaction. Such an electron transfer, which oxidizes the originally formed Co^{II} back to Co^{III} and reduces the alkyl radical to the carbanion $R^{\ominus}$, can also be observed in the photolysis of 1,19-dimethyl-*AD*-bis(dehydrocorrinato)cobalt(III) complexes[190].

Halomethylcobalamins prefer a third variant of the photodealkylation: the initially-formed alkyl radical stabilizes itself by decomposition to a halocarbene which can be trapped[178, 191].

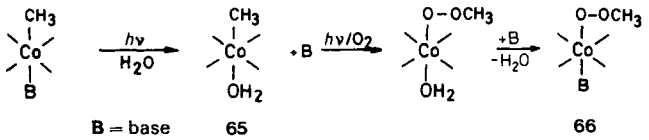
$$[Co^{III}]CHCl_2 \xrightarrow{h\nu} [Co^{II}] + Cl + :CHCl$$

In the presence of oxygen, the photolysis reactions of [Co]R follow a totally different course[192]: the diradical O_2 suppresses the reversible reaction

$$[Co^{II}] + {}^{\circ}R \rightleftharpoons [Co^{III}]R$$

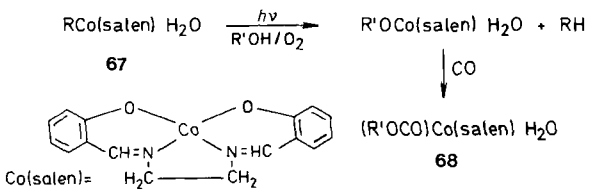
by undergoing subsequent reactions with one or both of the reaction products. Thus, photolysis of methylcobalamin in aqueous solution under aerobic conditions yields formaldehyde and aquo-Co^{III} complexes.

Cobaloximes insert a molecule of O_2 into the cobalt-carbon bond, generating peroxo complexes **66**[193, 194].



The mechanism proposed for this reaction differs from the previous reaction schemes in that its first step does not consist of a photoinduced dissociation of the cobalt-carbon bond, but rather of a loss of the base B from the metal. Only the aquo complex **65**, which is formed by coordination of water, undergoes the photoinduced dissociation[195]. The resulting methyl radical takes up dioxygen, and the radical ${}^{\circ}OOCH_3$ recombines with the Co^{II}-fragment to form the peroxo complex **66**, which can be isolated at low temperature. It is not yet clear why the homolytic bond cleavage is preceded by a photoinduced transformation into the aquo complex: the irradiation probably generates several competing excited states, and the most favored state leads to formation of **65**[178].

The photoinduced reaction of $RCo(salen)(H_2O)$ **67** (R = Me, Et, Pr, Bu) with carbon monoxide in the presence of oxygen in alcohols proceeds in a similar way via homolysis of the Co–C bond[196].



The radical ${}^{\circ}R$ stabilizes itself by hydrogen abstraction from the alcohol; the resulting ${}^{\circ}OR$ radical binds to $Co(salen)(H_2O)$. Only then does the insertion of CO into the newly formed cobalt oxygen bond occur to generate **68**. Apparently, the oxygen serves as a radical acceptor as well as an oxidant for $Co(salen)(H_2O)$. When O_2 is excluded from the reaction, CO insertion is not observed.

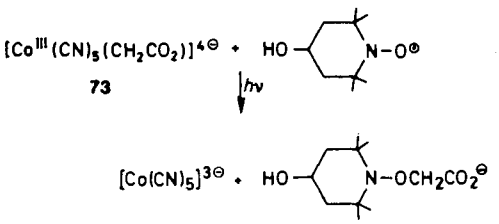
Also of note is the photolysis of **69**[197]. The homolytic cleavage of the cobalt-carbon bond is preceded by a photoinduced charge-transfer excitation benzyl→cobalt (LMCT). The benzyl radicals are stabilized by dimeriza-

$$2[Co(CN)_5(CH_2Ph)]^{3\ominus} \xrightarrow[\lambda = 313\ nm]{h\nu} 2[Co(CN)_5]^{3\ominus} + (CH_2Ph)_2$$
69 **70**

tion or—in the presence of oxygen—are trapped and form the addition product ${}^{\circ}OOCH_2Ph$, which binds to **70**, generating the peroxo complex **71**, which in aqueous solution decomposes to **72** and benzaldehyde.

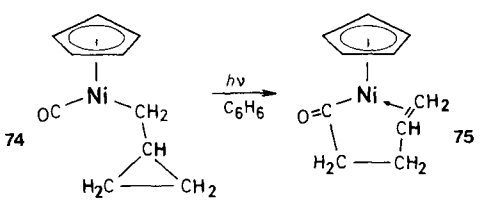
$$\mathbf{69} + O_2 \xrightarrow{h\nu} [Co(CN)_5(O_2CH_2Ph)]^{3\ominus}$$
71
$$\downarrow +H_2O$$
$$[Co(CN)_5H_2O]^{\ominus} + PhCHO + OH^{\ominus}$$
72

Similar photoreactions can also be observed with the complex **73**, which is especially suited to trapping nitroxides in biochemical reactions[198].



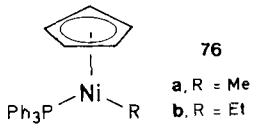
3.7. Photoreactions of Alkyl Complexes of Nickel, Palladium, and Platinum

Few studies exist on the photolyses of alkyl complexes of nickel. It is known that the cyclopropylmethylnickel complex **74** is converted by UV radiation into the light-stable metallacycle **75**[199].



A mechanism is proposed involving carbonyl insertion into the nickel-carbon σ-bond with synchronous opening of the three-membered ring and coordination of the resulting olefinic double bond.

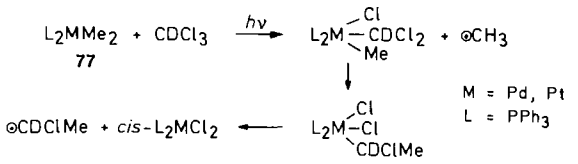
Photolysis of the methyl complex **76a** in benzene produces methane (96%) and ethane (4%)[200]. The hydrogen



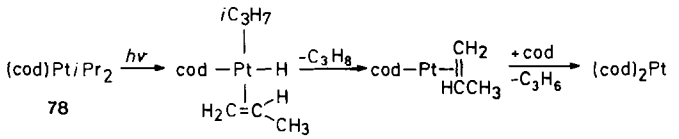
76
a, R = Me
b, R = Et

required for methane formation originates from the cyclopentadienyl ligand, other methyl ligands, and the solvent. Dimerization of methyl radicals seems to be responsible for the formation of ethane. Thermal decomposition of **76a** yields the same products[201], but in different relative amounts. The ethyl derivative **76b** is photodealkylated to form ethene and ethane, the β-hydrogen elimination being facilitated by the photoinduced dissociation of the phosphane ligand. No information is available on the metal-containing products of these photolyses.

Alkyl compounds of palladium and platinum are very stable to light in hydrocarbon solvents. In chlorinated solvents, however, they undergo alkyl-halogen exchange. On the basis of CIDNP experiments, the following mechanism is proposed for the photolysis of complexes **77**[202].



Surprisingly, photolysis of *cis*-L_2PtnBu_2 also involves radicals and does not proceed via β-hydrogen elimination, the mechanism followed by the thermal reaction[203]. UV irradiation of (cod)Pt*i*Pr$_2$ **78** in 1,5-cyclooctadiene (cod) leads to $(cod)_2Pt$[22]. Although the mechanism of this reaction has not been studied in any detail, a photoinduced β-hydrogen elimination seems to be a plausible initial step.

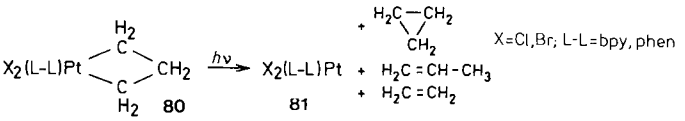


The trimethyl complex $CpPtMe_3$ **79** is photodealkylated via homolytic cleavage of the Pt–CH_3 bonds and formation of methane; the metal-containing product has not yet been characterized[204].

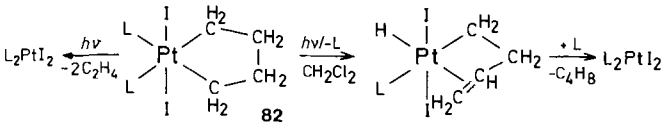
$$CpPtMe_3 \xrightarrow{h\nu} CpPtMe_2^{\odot} + {}^{\odot}CH_3$$
79

In this reaction, methyl radicals can be detected by ESR spectroscopy and trapping reactions; α-hydrogen abstraction and radical dimerization are negligible. The cyclopentadienyl ligand, methyl ligands, and the solvent serve as hydrogen sources for the formation of methane. Also interesting is the photolysis of the metallacycle **80**[205,206], since such four-membered ring systems are considered to be intermediates in olefin metathesis.

The reaction course proposed consists of simultaneous cleavage of the platinum-carbon and carbon-carbon bonds, which could produce cyclopropane or ethene, respectively. The formation of propene seems to arise from hydrogen transfer between adjacent methylene groups, but could also derive from a β-hydrogen elimination, which would generate an η^3-allyl(hydrido) intermediate. The latter compound loses propene to form **81**. The solvent is of great importance for the stabilization of the various intermediates.

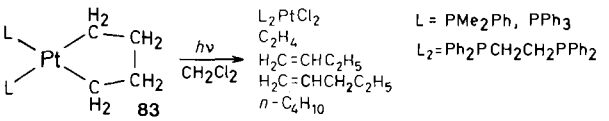


Photolysis of the five-membered metallacycle **82** in dichloromethane yields exclusively 1-butene and ethene[206].



Whereas the formation of ethene can be explained by a photoinduced ring fragmentation, 1-butene is unambiguously formed by a photoinduced β-hydrogen elimination. This is also observed in the photolysis of the related nickel complexes $L_3NiCH_2CH_2CH_2CH_2$ ($L = PR_3$, $PArYl_3$)[207].

The photoinduced decomposition of the platinum(II) complexes **83** via simultaneous homolysis and β-hydrogen elimination leads to *n*-butane and olefins.



The solvent is held responsible for the formation of 1-pentene; it provides a methylene ligand for the dealkylation, which causes the ring expansion.

The complexes **84**–**87** can be dealkylated in dichloromethane by UV light[208]. The scission of the platinum-carbon bond occurs irrespective of the number of alkyl ligands. The methyl radicals stabilize themselves by hydrogen abstraction from methyl ligands, other ligands, and the solvent.

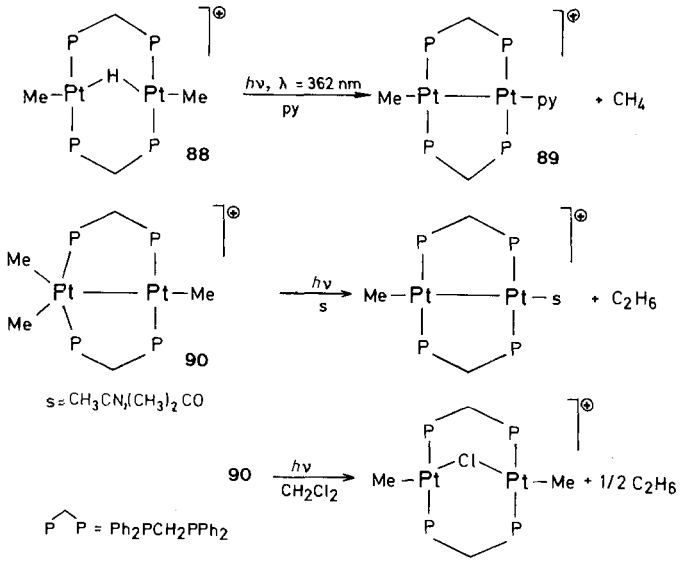
$$IPtMePh_2(bpy) \xrightarrow{h\nu} CH_4,\ C_2H_6,\ C_6H_5CH_3,\ Ph_2,\ PtIPh(bpy)$$
84

$$I_2PtMe_2(bpy) \xrightarrow{h\nu} CH_4,\ C_2H_6,\ PtI_2(bpy)$$
85

$$IPtMe_3(bpy) \xrightarrow{h\nu} CH_4,\ C_2H_4,\ PtIMe(bpy)$$
86

$$IPt(CD_3)_3(bpy) \xrightarrow{h\nu} CD_4,\ CD_3H,\ C_2D_4$$
87

Photolysis of **88** in pyridine leads to alkane elimination and formation of **89**, whereas **90** in acetone, acetonitrile,



or methylene chloride, reductively eliminates mainly ethane[209].

3.8. Photoreactions of Alkyl Complexes of Silver and Gold

The photochemistry of alkyl complexes with metals of group IB is largely undeveloped. **91** provides a good example for the observation that upon UV-irradiation some complexes undergo homolytic metal-carbon bond cleavage despite the availability of β-hydrogen[210].

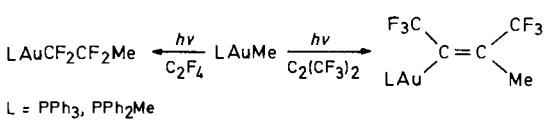
$$n\text{BuAgP}n\text{Bu}_3 \xrightarrow{h\nu} n\text{-}C_8H_{18}, n\text{-}C_4H_{10}, H_2C{=}CHC_2H_5, P n\text{Bu}_3, \text{Ag}$$
91

The photolysis of the analogous gold(I) compound **92** also involves radicals[211]. On the basis of CIDNP studies, UV irradiation excites the molecule into a singlet state, which undergoes intersystem crossing to an excited triplet state and from there reacts with the solvent $CDCl_3$.

The methyl radicals can undergo further reactions which generate CH_3D, C_2H_6, CH_3CDCl_2, and CH_3CCl_3.

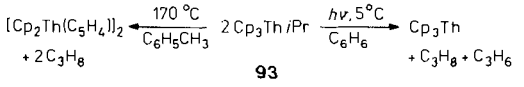
$$[Ph_3PAuMe]^T \xrightarrow[CDCl_3]{h\nu} Ph_3PAuCl + [{}^{\circ}Me + {}^{\circ}CDCl_2]^T$$
92

Potential ligands such as the fluoroolefins C_2F_4, C_3F_6, and C_2F_3Cl as well as hexafluorobutyne can be photochemically inserted into the Au–C bond[212].



3.9. Photoreactions of Alkyl Complexes of Thorium and Uranium

The difference between thermal and photochemical reactions is illustrated by the dealkylation of Cp_3ThiPr **93**[213].



Whereas the thermal decomposition involves radicals[214], the photochemical dealkylation proceeds via β-hydrogen elimination. The free coordination site, which is required on the metal, is probably provided by a photoinduced "ring slippage" ($\eta^5 \rightarrow \eta^3$) of a cyclopentadienyl ligand.

In contrast to **93**, photolysis of the analogous uranium compound Cp_3UR (R = *i*Pr, *n*Bu) **94** does not involve β-hydrogen elimination of the alkyl ligand but follows almost exclusively a radical pathway[215,216].

$$Cp_3U n\text{Bu} \xrightarrow[THF]{h\nu} Cp_3U(THF) + C_4H_{10} + C_4H_8$$
94a 93% 7%

The hydrogen required for alkane formation is provided by the cyclopentadienyl rings and the solvent. The surprising course of the reaction can be ascribed to the different redox potentials.

$$U^{IV} \longrightarrow U^{III}: -0.63\ V$$
$$Th^{IV} \longrightarrow Th^{III}: -3.7\ V$$

Uranium(IV) is much more easily reduced than thorium(IV). Another reason could be that the "ring slippage" mechanism, which provides the open coordination site on the metal, does not occur readily with uranium complexes.

4. Summary and Prospects

From the above excursion through the photochemistry of alkyltransition-metal complexes it is evident that this embryonic branch of organometallic chemistry has opened multifaceted preparative possibilities. The main advantage offered by photochemical compared to thermal reactions is that the former can be initiated and monitored spectroscopically, irrespective of the temperature. A whole series of highly reactive compounds and fragments such as alkene(hydrido) and alkylidene(hydrido) complexes, and free carbenes and alkyl radicals can be continuously generated in situ and used for preparative or catalytic reactions.

Photochemical methods nevertheless retain a hint of "alchemy" since for many alkyl complexes too little is known about what occurs in a given molecule after absorption of a quantum of light and what physical processes occur along the path to the primary chemical product. Even slight electronic changes in the complex, use of different solvents, or variation in the wavelength of the radiation can produce completely different reactions, indicating very sensitive and easily influenced processes. The combined use of physical methods such as flash photolysis, ESR, NMR (CIDNP), and IR spectroscopy may "throw more light" onto the nature of the primary and secondary processes. In the future, more attention must be given to the selective excitation of molecules through the use of mono-

chromatic light sources (lasers). Theoreticians are challenged too! Calculations on suitable model compounds may some day allow predictions to be made about the course of photodealkylations.

What can the preparative chemist expect? Today, a large number of attractive alkyltransition-metal complexes resemble "sleeping beauty", waiting to be awakened by UV light. The knowledge gained from the alkyl complexes should also be applicable to other σ-organyl complexes, e.g. acyl or aryl coordination compounds, which have been little studied. In this context, photolysis of the aryl complex Cp_2ZrPh_2[217] should be mentioned. The photochemically generated Cp_2Zr fragment can be used for a number of preparative reactions[218].

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Chiral Macrocycles as Reagents and Catalysts**

By Richard M. Kellogg*

Ionophores, whether of natural or synthetic origin, encapsulate their ionic "guests" using noncovalent bonding. This encapsulation process resembles, at least superficially, the bonding of a substrate by an enzyme-active site. The analogy to enzymes can be extended further if the ionophore is provided with functional groups that can react with a suitable guest molecule bound in the cavity of the ionophore. We have embedded in the periphery of a macrocycle a 1,4-dihydropyridine, a mimic of the coenzyme NADH. The macrocycle, in addition to having (weak) ionophoric properties, is chiral. This strategy has led to compounds that react as artificial hydrogenases and which are capable of distinguishing, in a predictable fashion, between the prochiral faces of suitable carbonyl substrates. Ancillary developments from this approach have been many. A remarkably general method for the preparation of a wide variety of macrocycles has been developed which depends on some remarkable chemical idiosyncrasies of the cesium ion. In attempts to exploit the chemical possibilities of these macrocycles, unusual chemistry, possibly relevant to the action of the enzyme, 3-phosphoglyceraldehyde dehydrogenase, has been uncovered. In a similar vein, study of macrocycles has led to variants of the aldol condensation on chiral templates. Finally, catalytic CC bond formation mediated by transition metals is revealed to be an area in which chiral macrocycles can play a useful role by acting as chiral ligands for the transition metal.

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1. Introduction

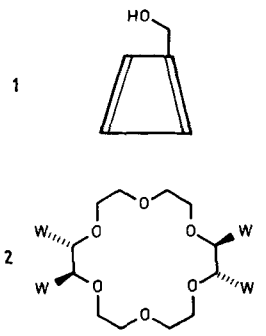
The architectural possibilities offered by synthesis together with the predictive power of mechanism can be harnassed for the design of molecular catalysts. A designed

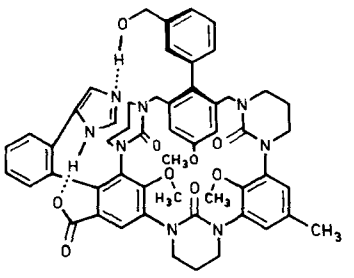
molecular catalyst might reasonably be expected to be capable of recognizing a substrate, inclusive of its chirality; to be complementary to the transition state of the reaction it catalyzes[1]; and to discharge the products after reaction and regenerate itself. These, and other functions, are, of course, achieved by those wonders of nature, enzymes, which accomplish their purpose, however, with the aid of frightening molecular complexity. It occasions little surprise that chemists interested in designing molecular catalysts do so, on the whole, by combining some inspiration drawn from enzymes, chiefly the active site, together with the enormous body of chemical knowledge drawn from other sources. It is unlikely that the products of such inspiration will approach in any degree the molecular complexity of most enzymes. Nor is it necessary that they do so.

Whatever the sources of inspiration, one thing that must be controlled is *noncovalent bonding*. This stems from the consideration that a catalyst can best have at least some of the aspects implicit in the classical Michaelis-Menten kinetic equation [eq. (a)][2]. The catalyst, in general, will have to complex with the substrate in an enzyme-like fashion and hold it in a defined orientation. This requires mastering the complexities of noncovalent bonding.

$$\underset{\text{(M)}}{\text{Enzyme model}} + \underset{\text{(S)}}{\text{Substrate}} \rightleftharpoons [\text{M}\cdot\text{S}] \longrightarrow \text{M} + \text{Product} \qquad \text{(a)}$$

One well-known route to molecular catalysts which illustrates clearly many of these considerations uses the naturally occurring cyclodextrins. **1** shows a schematic side view of the torus formed by these cyclic glucose oligomers: the smaller end is rimmed with primary hydroxyl groups and the larger end bears the secondary hydroxyls of the pyranose rings. A "substrate" is extracted from aqueous solution into the hydrophobic cavity, but once there the guest molecule is free to move within the constraints provided by the walls[3].





3

Particularly *Breslow*[4] and *Tabushi*[4] have developed methods of introducing catalytic groups via the hydroxyl moieties onto the rim of the cyclodextrin; these catalytic groups can operate in an enzyme-like fashion on a suitable encapsulated substrate.

Crown ethers such as **2** are, on the other hand, totally synthetic in origin. The predesigned cavity complexes rigidly, through three of the oxygen atoms, the three hydrogens of an ammonium ion $RNH_3^{\oplus}$, as shown elegantly by *Cram*. Functionalized "arms" (indicated as "W") at suitable positions on the periphery can react with substituents R on the bound ammonium ion, as described by *Lehn* et al.[5].

A lovely molecular design is **3**, a model for a protease designed by *Cram* et al.[6], but not yet completely synthesized. The "spherand" structure provides, via the amide oxygens, a prestructured cavity for the firm encapsulation of an ammonium ion. An ester or amide incorporated at the proper position of the R group of the encapsulated $RNH_3^{\oplus}$ can be acted on in an enzyme-like fashion by the surrogate groups about the periphery which mimic the serine hydroxyimidazole-aspartate combination of hydrolases such as chymotrypsin.

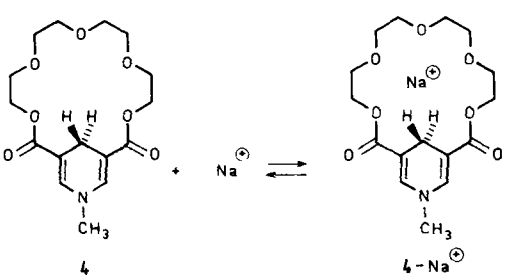
Compounds **1**—**3** are popular models for enzymes. Many variants can, and have been, thought of and realized. We will concentrate here chiefly on molecules into which, by rational synthesis (combined, if possible, with the structural bounty offered by Nature in the form of cyclodextrins, amino acids, etc.), a great deal of structural information has been incorporated in advance for regulation of noncovalent bonding to attach the substrate and possible activating ions or neutral molecules. The results are a blend of organic and inorganic chemistry that may, in certain cases, be significant for understanding related enzymic systems. Be that as it may, the results are interesting and useful in their own right as an extension of existing chemistry.

2. Enantioselective Reductions with Chiral Bridged 1,4-Dihydropyridines

In view of the introductory remarks, we have tried to use macrocycles as "templates" for chemical reactions. This was inspired, in part, by the imaginative work on "crown ethers", "cryptands", and cyclodextrins just discussed[7]. We have incorporated reactive functionalities into or onto the macrocycle and have used the enforced geometry and complexing ability to direct reactions on this macrocyclic template. The functionalities used so far have been chiefly related to coenzymes, in particular the redox couple $NAD(P)^{\oplus}/NAD(P)H$[8].

At the outset it should be emphasized that a major barrier we have encountered, even more serious than those problems associated with molecular design, is incomplete mechanistic knowledge and the occurrence of unique chemistry, which was not (or, in my opinion, could not) be predicted a priori.

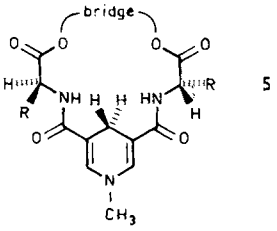
Some initial experiments were carried out with **4**, in which a Hantzsch 1,4-dihydropyridine has been included



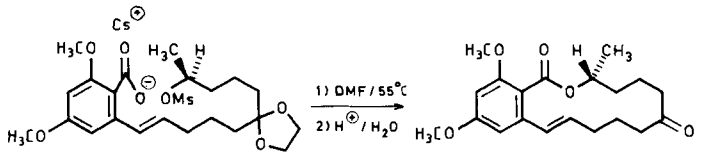
4 4-$Na^{\oplus}$

in the periphery of an 18-crown-6 macrocycle. The distortion of the periphery lowers the affinity towards cations as compared to 18-crown-6, but nevertheless complexation does occur to give isolable salts with $NaClO_4$ (and a mole of solvent)[9].

Although **4**-$Na^{\oplus}$ displays no enhanced reactivity, this observation encouraged us to try to improve the design. We were further encouraged by the fact that **4** rapidly reduces certain sulfonium salts after prior complexation of the sulfonium ion[10]. A reasonable synthetic goal was the general structure **5** in which chirality has now been built in by virtue of the inclusion of the two identical amino acids. As long as the structure of the bridge is symmetrical, a C_2 axis is present in the molecule. The two faces of the 1,4-dihydropyridine are equivalent and the hydrogens at the 4-position are homotopic, not diastereotopic, as in NAD(P)H.

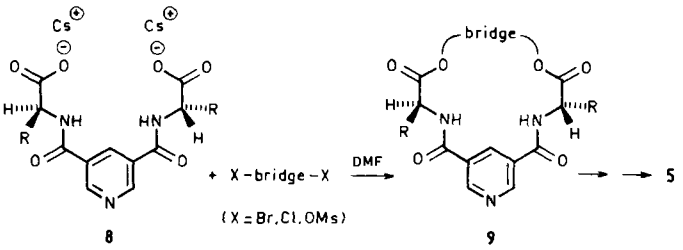


Before the rationale behind the choice of **5** is discussed, a pragmatic question of synthesis of such macrocycles must be addressed. We had, in connection with similar problems, developed a method based on the use of cesium salts to promote macrocycle formation via an anionic S_N2 substitution as the ring closure step. This technique works especially well for those cases where the probability of a "template effect" with a cation is less due to the absence of properly disposed heteroatoms in the open-chain compound to be cyclized. An illustration of this "cesium effect" is provided by the synthesis of (*R*)-zearalenone dimethyl ether **7** from (*S*)-**6**, a reaction which proceeds in 80% yield with the expected inversion at the secondary carbon atom[11]. Similar encouraging results are found for the



syntheses of a wide variety of macrocyclic lactones. This unanticipated behavior of cesium cations is thought to be related to the special properties of a "tight ion pair" formed in dimethyl formamide (DMF)[11,12]. The properties of these ion pairs are currently being studied by ^{133}Cs-NMR spectroscopy[13].

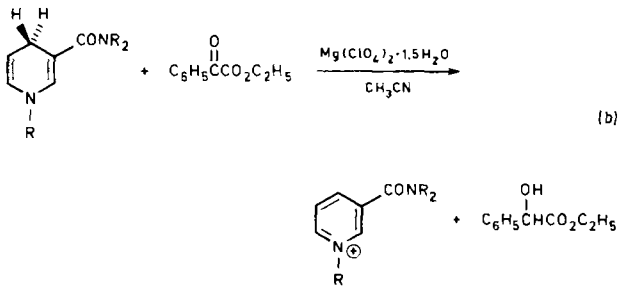
Application of the "cesium salt" method enables also the synthesis of *di*lactones such as **9**, which by further routine transformations can be converted into **5**. The restrictions are that the bridge is at least four atoms long (17-membered macrocyclic ring is formed) and that the terminal C atoms of the bridge are (preferably) primary so as to ensure smooth S_N2 displacement and the absence of additional stereochemical problems. Valine (the natural L-enantiomer is shown in the formula) has been used most ex-



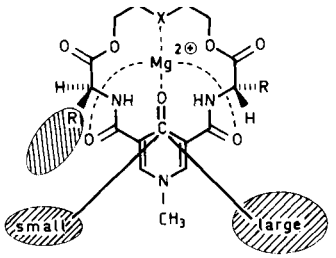
tensively because of its good solubility and polarity properties. Phenylalanine, alanine, and proline have been used to obtain supplementary information. Compounds derived from phenylglycine have been prepared, but problems with partial racemization have been serious[14].

Rather than present extensive lists of compounds and results, I will try to illustrate the main points that have emerged from the study of these compounds. Exhaustive coverage of details is available elsewhere in the literature[14].

Let us return to the rationale behind the use of **5**. Consider first enantioselective reductions. Other groups had established that in the presence of metal ions, (especially $Mg^{2\oplus}$) activated carbonyl compounds (e.g., alkyl phenylglyoxylate esters) are reduced by 1,4-dihydronicotinamide derivatives [Eq. (b)][15].



Even after extended drying, the metal salt $Mg(ClO_4)_2$ contains ca. 1.5 equivalents of H_2O. *Ohno* et al.[16] have elegantly demonstrated that in several cases high transfer of chirality could be obtained with 4-methylated-1,4-dihydropyridines if the carboxamide side chain is substituted with an (optically pure) amino acid. We thought that it would be advantageous if a ternary complex could be formed in which the $Mg^{2\oplus}$ ion were held in a defined position in the macrocycle **5**. The carbonyl oxygen atom of the phenylglyoxylate to be reduced should be coordinated to $Mg^{2\oplus}$ and lie on the macrocyclic surface, as illustrated in Scheme 1, to minimize steric interactions, while placing the carbon atom to be reduced in a stereoelectronically reasonable position relative to the 4-position of the 1,4-dihydropyridine[17]. The amino acid substituents, related by a C_2 opera-

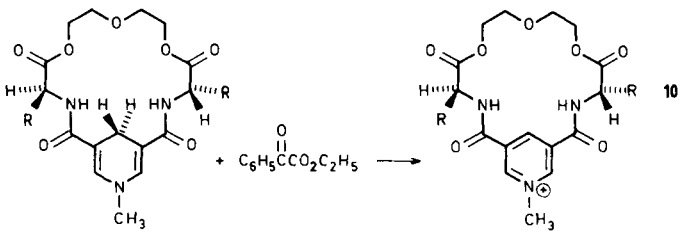


5-$Mg^{2\oplus}$-ketone

Scheme 1. Structure of the ternary complex 5-$Mg^{2\oplus}$-ketone.

tion, provide a steric barrier which influences the face selectivity of binding of the carbonyl group. This type of coordination entails an out-of-plane movement of the macrocyclic ring to allow the carboxamide groups to complex. Although this model turns out to be over-idealized, its predictive power, especially in terms of the absolute configuration of the alcohol formed, is indeed remarkable.

The chiral recognition is predicated from the steric effects that arise from the amino acid substituents. That these substituents—none of which are large—have an effect is nicely illustrated by the comparison in Scheme 2[14,18]. A macrocycle into which an (*S*)-amino acid has

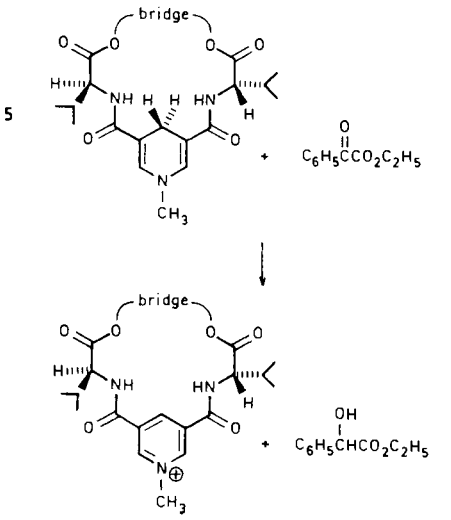


R	*ee* [%]	config.
CH_3	61	*S*
$C_6H_5CH_2$	86	*S*
$(CH_3)_2CH$	87	*S*

Scheme 2.

been incorporated provides the (*S*)-enantiomer of ethyl mandelate. There are, however, no significant accelerations in rate relative to the nonbridged analogues. The enantiomeric excesses for these room-temperature reductions are quite good, and, as seen from inspection of the complex 5-$Mg^{2\oplus}$ ketone, are also in accord with the predictions of our simple model that the *re*-face of the carbonyl group should be attacked since phenyl is the "large" group.

This general picture, and, in particular, this overall stereochemical result, is even more convincingly established when the size and shape of the bridge bearing the amino acid "arms" are varied. The enantiomeric excesses with $R=(CH_3)_2CH$ for polymethylene bridges of successively greater length are shown in Scheme 3. The enantiomeric excesses remain excellent up to and including eight methylene groups in the bridge before beginning to decline. And even for the dodecamethylene bridge, a compound with a 25-membered macrocyclic ring, chirality is still transferred with surprising faithfulness and with the same stereochemical bias. The reaction appears to proceed via a rather generally applicable mechanism.



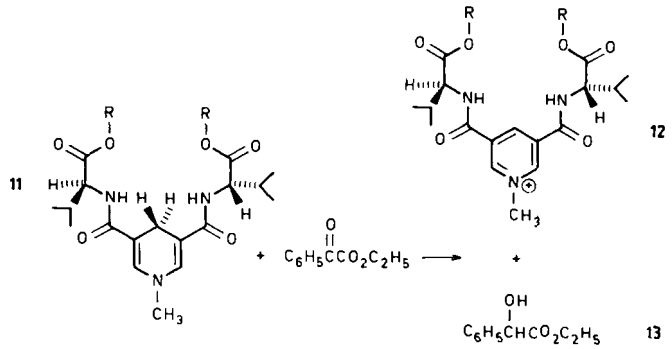
bridge	*ee* [%]	config.
$(CH_2)_5$	90	*S*
$(CH_2)_6$	88	*S*
$(CH_2)_8$	82	*S*
$(CH_2)_{10}$	52	*S*
$(CH_2)_{12}$	42	*S*

Scheme 3.

This impression that general principles can be involved in all these reductions is strongly reinforced by the fact that we have not observed a single exception to the above mentioned stereochemical pattern for all the 28 chiral bridged 1,4-dihydropyridines which we have synthesized and examined, and in which length, composition, and shape of the bridge have been extensively changed

Some additional points deserve to be mentioned, however, before an attempt is made to define general principles. One is that the two arms must be locked together by a bridge to obtain adequate transfer of chirality. Some typical results for nonbridged compounds are shown in Scheme 4. Apparently in these cases the "side arms" can assume a variety of conformations from which reactions can occur[19]. When the conformations are locked by joining the arms with a bridge, greatly improved chiral recognition results.

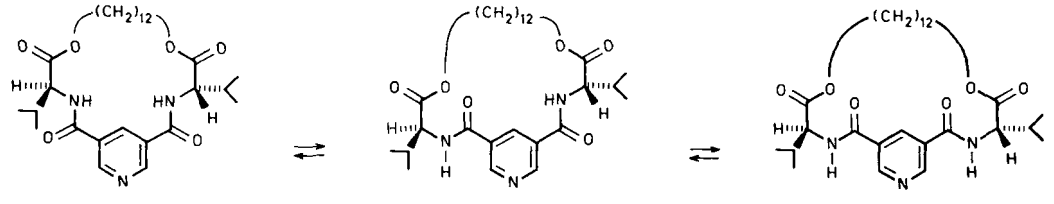
One must realize, however, that a bridge does not provide a total conformational lock. The conformations of these macrocyclic compounds, with their great variation in bridge lengths, can differ greatly. Some factor must operate to provide a conformational bias. This point can best



	ee [%]	config.
a, $R = CH_3$	10	*R*
b, $R = CH_2CH_2OCH_3$	18	*R*

Scheme 4.

be illustrated with compound **9**, which has the greatest degree of conformational mobility. There are three minimum energy conformations for this compound (Scheme 5):



inside / inside — outside / outside — outside / outside

9 (bridge = $(CH_2)_{12}$)

Scheme 5.

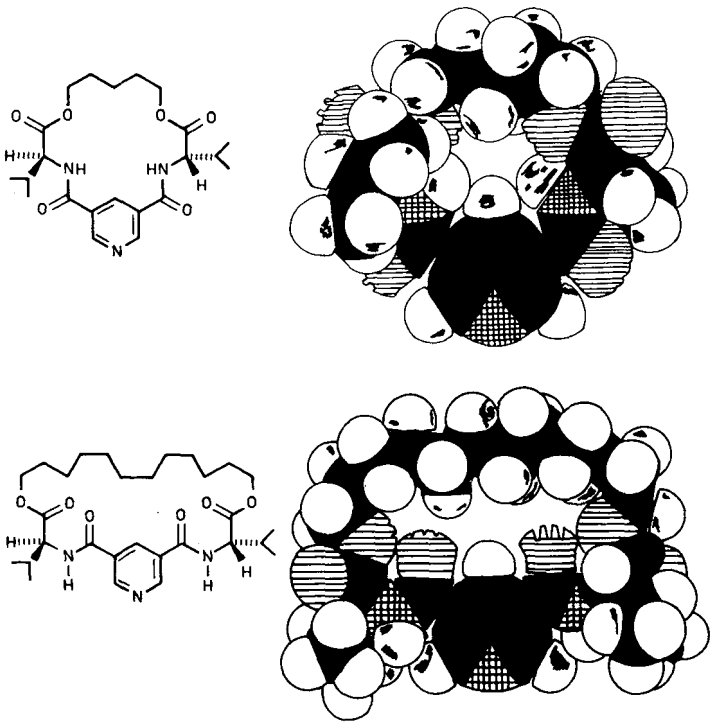


Fig. 1. Space-filling model (right) of the favorable conformations of an inside/inside and outside/outside conformation of two pyridine macrocycles. In the space-filling models the view is from the top; the pyridine nitrogen and the amide nitrogens are crosshatched.

one with both amide hydrogens inside the macrocycle (inside/inside), another in which the entire amide has rotated 180° about the carbonyl-ring bond (inside/outside), and a third conformation in which both amide groups have rotated (outside/outside). We assume that the amide units will not deviate from the *trans*-conformations indicated. There are adequate grounds to support this assumption. The inside/outside and outside/outside conformations are only attainable for bridges of length 10 atoms or more; otherwise, the compound is held in the inside/inside conformation with only restricted possibilities for further external conformational motion owing to the rigidity of the amide functionalities and the aromatic ring. These arguments are based on the results of temperature-dependent circular dichroism and ^{13}C-NMR measurements[20]. Measurements were carried out on pyridines **9** for stability reasons, but the same arguments apply also to 1,4-dihydropyridines **5**.

The inside/outside and outside/outside conformers have morphologies which are strongly at variance with those of the inside/inside conformer, in particular with respect to the placement of the chiral barriers, which effect the chirality recognition. (A comparison of bridged pyridines and 1,4-dihydropyridines has just been made. The latter are in general too unstable to allow conformational studies. There is, however, little reason to believe that the steric situation for a bridged 1,4-dihydropyridine is fundamentally different from that in pyridines.) The fundamental differences in morphologies of the various conformers are illustrated in Figure 1. Why is this difference not reflected all that strongly in the enantiomeric excesses obtained when these macrocycles are used as reagents for the reduction of prochiral carbonyl compounds?

Still another point must be made: The stability constants of these macrocycles with $Mg^{2\oplus}$ ions are not large. As can be seen from the data in Figure 2, a heavy debt in complexing power (but not so much so in enantioselectivity) has been paid for the extensive modification of the macrocyclic periphery.

The $Mg^{2\oplus}$ ion, a powerful electrophile, must have the cardinal function of organizing the structure of the macrocyclic system, as shown in Figure 3. The $Mg^{2\oplus}$ ion associates with the oxygen atom of an amide group; at the same time, it acts as an electrophile towards the carbonyl group to be reduced. If we confine ourselves to phenylglyoxylate esters as substrates, we expect that this carbonyl-$Mg^{2\oplus}$ unit will orient itself *trans* to the amino acid substituent. In Figure 3 this is indicated by complexation on the right-hand side of the molecule (an arbitrary choice since the amides are related by a C_2 axis in the uncom-

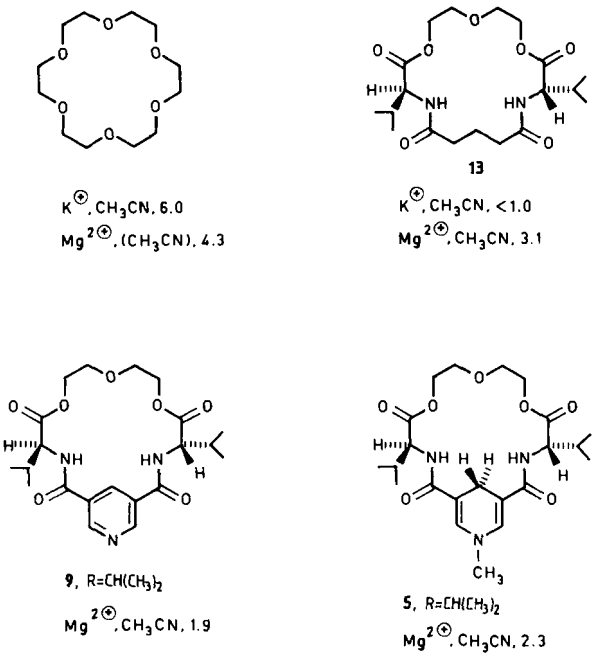


Fig. 2. Comparison of the complexing ability of various compounds. For **5**, **9**, and **13** the association constants were determined conductometrically. The value for 18-crown-6 with $K^{\oplus}$ was measured by H. K. Frensdorf (*J. Am. Chem. Soc. 93* (1971) 600). The cation is shown first, followed by the solvent and $\log K_{ass}$.

plexed macrocycle). On complexation, the C_2 axis is lost. Reduction requires replacement of the carbonyl carbon atom above the 4-position of the 1,4-dihydropyridine. This can be achieved only by placing the carbonyl substituents "astraddle" the chiral barrier on the left-hand side of the molecule. Examination of CPK models shows that the phenyl ring must indeed be oriented over the dihydropyridine moiety[21].

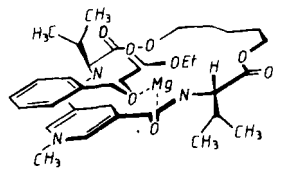


Fig. 3. View of the ternary complex that is presumed to be the intermediate in the reduction.

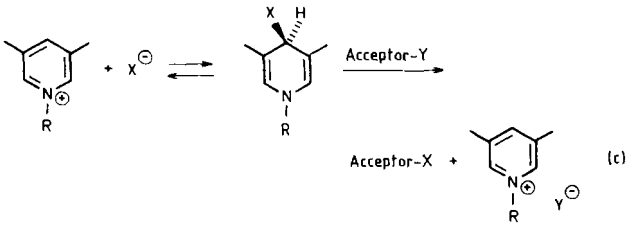
The orientation shown in Figure 3 differs from the original model **5**-$Mg^{2\oplus}$ complex in that complexation with the bridge is not involved, as established unequivocally by structure-reactivity studies. In Figure 3 the carbonyl group is rotated about 90°, but the *re*-face of the carbonyl group is still that exposed for acceptance of "hydride".

The essential point is that $Mg^{2\oplus}$, although it complexes only relatively weakly, organizes the structure of the macrocycle; this is accomplished by noncovalent forces. Such organizational effects are quite common in chemistry, although not often so dramatically apparent as here.

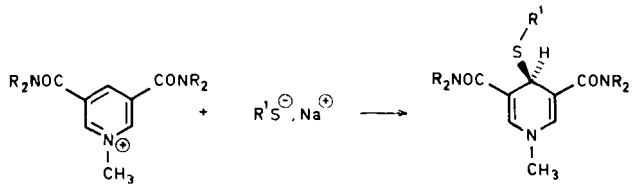
3. The Problems of Ion Pairing in Pyridinium Ion/Thiolate Adducts

With these bridged chiral macrocycles in hand, we now searched for other applications in addition to the reductions described. One could, in general, inquire to what extent a pyridinium salt (or for that matter other aromatic, positively charged heterocycle) possesses a wider ligand-transfer ability. This is illustrated schematically in equation (c). All the anions $X^{\ominus}$ shown have been reported to add to pyridinium salts[23].

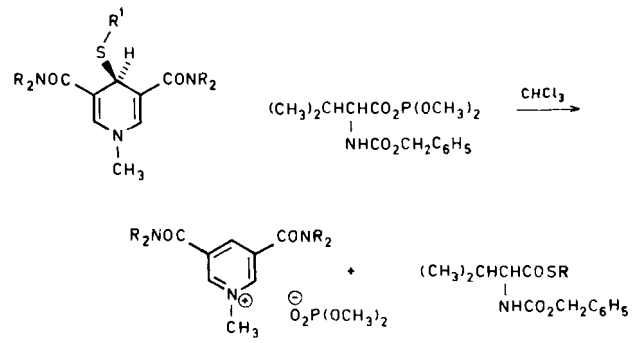
In order to simplify matters, the anion $X^{\ominus}$ is assumed to add only to the 4-position[22]. X is initially present as an anion in the reaction and is then transferred to a substrate (acceptor X). Are there any advantages to be gained from this circuitous pathway? Certainly for transfer of "hydride" there appear to be; this is, of course, the general function of the $NAD^{\oplus}$/NADH(H) coenzyme couple!



Pyridinium salts **14** from amides of pyridine-3,5-dicarboxylic acid, the basic building block of the macrocycles **9**, also undergo clean, regioselective addition of thiolate to provide covalent adducts of the general structure **15**.



Under completely neutral reaction conditions the adducts **15** transfer smoothly, via the covalent forms, the thiolate group to, for example, activated esters to form thioesters. This possibility is illustrated for the synthesis of an amino acid thioester in Scheme 6[23h]. Purification of the



Scheme 6.

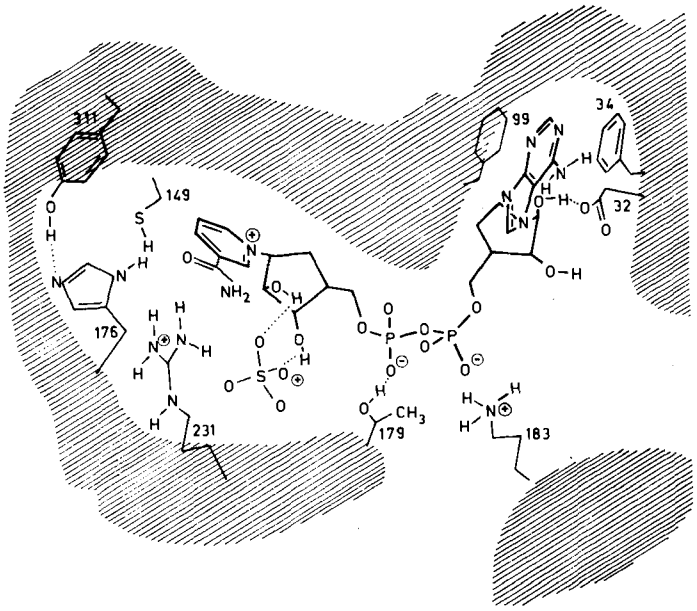
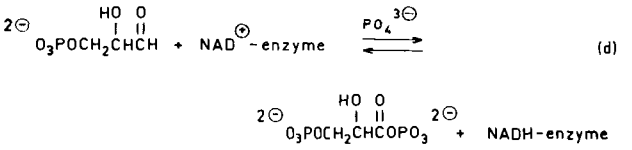
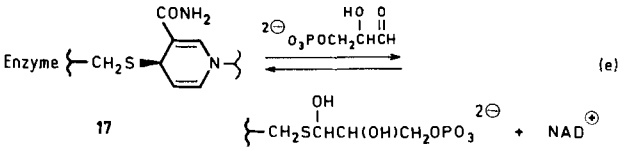


Fig. 4. View of the active site of 3-phosphoglyceraldehyde dehydrogenase with bound NAD⊕. Reproduced with kind permission of the publishers from *M. Rossmann* et al. in P. Boyer: *The Enzymes, Vol. 11*, Academic Press, New York 1975, p. 87.



(d)

of groups at the active side is illustrated in Figure 4. The enzyme catalyzes the overall oxidation of 3-phosphoglyceraldehyde to the acyl phosphate [eq. (d)]. The initial product is, however, an acyl ester with Cys-149, which is transphosphorylated at a second active site of the enzyme. The essential reaction scheme is given in Figure 5[24]. If, however, Cys-149 were first to add to NAD⊕, **17** would be formed. If this compound is to be a viable intermediate, however, there must be a pathway for its conversion into



(e)

thioesters is especially easy because the only side product is the polar pyridinium salt. In the case of chiral bridged pyridinium salts, this type of reaction offers the possibility of transfer of thiolate under asymmetrie conditions. Various ways of realizing this idea can be envisaged. The unexpected over whelmed us at this point, however.

the hemithioacetal intermediate shown in Figure 5 [see eq. (e)].

This proposed thiolate addition to NAD⊕ is not original. It was first made more than thirty years ago by *Racker* and *Krimsky*[25]. This idea seems, however, to have fallen by the wayside in favor of charge-transfer explanations of

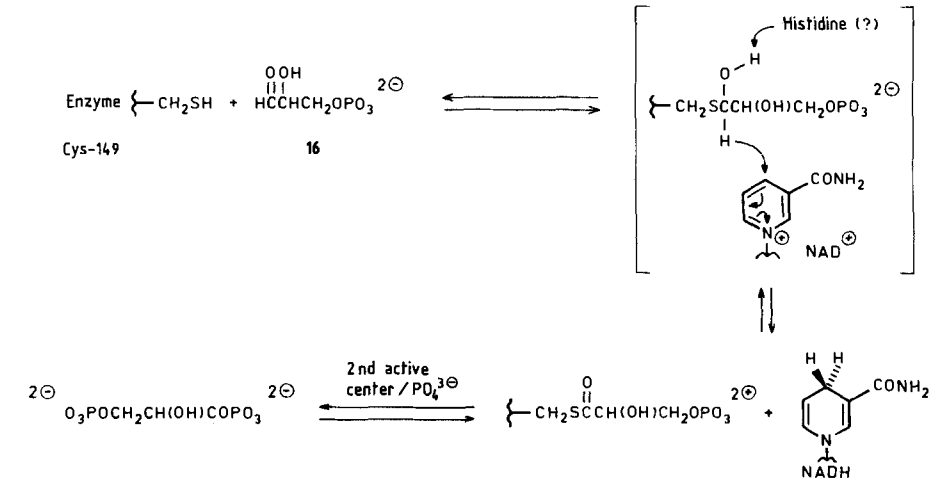
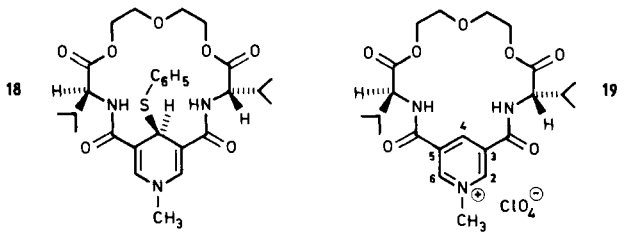


Fig. 5. Mechanism of the reaction of glyceraldehyde 3-phosphate with glyceraldehyde 3-phosphate dehydrogenase.

But before describing this in detail, we shall make a small detour into biochemistry. Thiolate addition to a pyridinium salt, NAD⊕ to be specific, could be significant in the mechanism of action of the enzyme glyceraldehyde phosphate dehydrogenase. At the active site of this enzyme there is a reactive cysteine (Cys-149), which, together with its catalytic action, is involved in the formation of the yellow color characteristic of this enzyme. The arrangement

the yellow color[26]. It is striking, however, that the long-wavelength maximum for the NAD⊕-3-phosphoglyceraldehyde dehydrogenase complex from rabbit muscle has $\lambda_{max} = 360$ nm, whereas **18**, a compound that will figure in subsequent discussions, has $\lambda_{max} = 340-350$ nm, depending on the solvent[27]. The UV spectra of **18** are representative for the thiolate addition products from 3- or 3,5-mono or disubstituted carboxamidopyridinium salts in general[27].



I return now to the unexpected: The ^{1}H- and ^{13}C-NMR spectra (and abnormal reactivity behavior, which first led to a close examination of the spectra) of **18** and related compounds, including examples without a bridge, are found to have a puzzling dependence on solvent. The most important aspects of the NMR spectroscopic behavior are summarized in Figures 6 and 7, which show the solvent-dependent ^{1}H- and ^{13}C-NMR absorptions at room temperature. No attempt has been made to reproduce temperature-dependent behavior. The spectroscopic behavior in CD_3OD is also similar to that in CD_3COCD_3, CD_3CN, and CD_3SOCD_3. Of note is that, on dissolution in a polar solvent, the signals for C-4 and H-4 have a pronounced

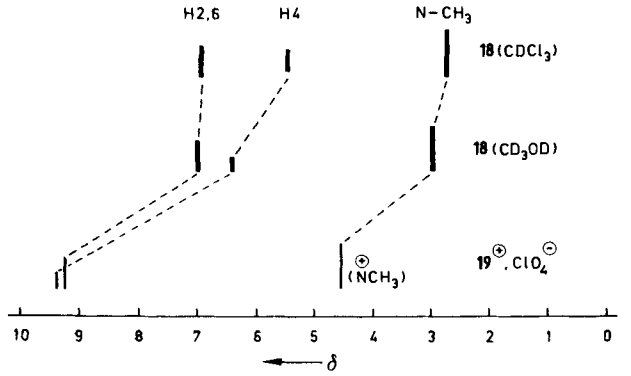


Fig. 6. Solvent-dependent ^{1}H-NMR signals (all other signals have been deleted for clarity) of **18** in $CDCl_3$ (top) and in CD_3OD (middle), as compared to the signals of the pyridinium salt **19** (bottom). In polar solvents the signals of N–CH_3, H-4, and H-2/H-6 of **18** shift in the direction of the corresponding signals of **19**. Full details are given in [27].

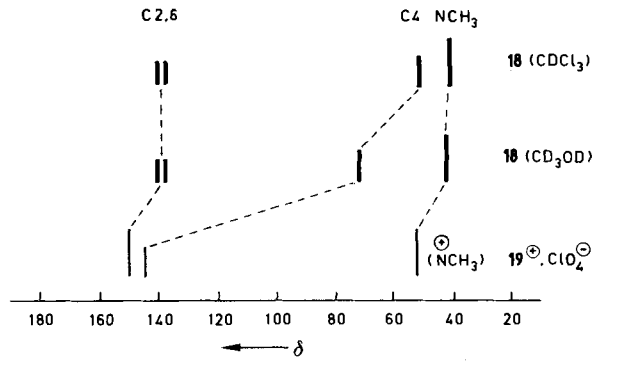
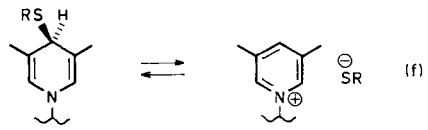


Fig. 7. Solvent-dependent, proton-decoupled ^{13}C-NMR signals of N–CH_3, C-4, and C-2/C-6 in $CDCl_3$ (top), CD_3OD (middle) compared with those of the pyridinium salt **19** (bottom). All other absorptions have been deleted for clarity. Full details are available in [27]. Note for C-2 and C-6 that the effect of the diastereotopicity of these carbons (and the attached protons) can just be observed.

tendency to shift downfield towards the characteristic absorption positions of the signals of pyridinium salts. The effect is smaller for C-2, C-6, H-2, H-6, and NCH_3.

There could be a reasonable, and not particularly surprising, explanation for this behavior. The adducts with thiolate are clearly covalent in solvents such as $CDCl_3$, but they might ionize partially in more polar solvents to give a pyridinium/thiolate ion pair [eq. (f)]. If the concentration



of thiolate is low and the rates of dissociation and recombination are, within an order of magnitude, comparable with the NMR time scale, a simple and not especially dramatic explanation of the spectroscopic analomies might be at hand.

This is, however, not the case. We have shown[27] for **18** and related compounds that

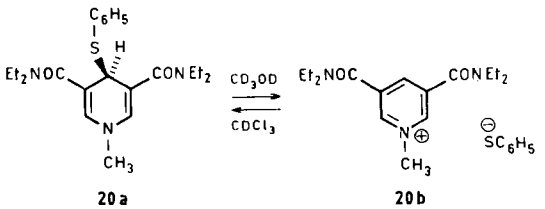
a) Thiolate does not dissociate from the pyridine to which it is originally bonded. No "crossover" of thiolates from one molecule to another has been detected, as would be expected with the ion pair in equation (f).

b) No appreciable change in the magnitude of $^1J_{^1H,^{13}C}$ of C-4 in **18** (ca. 150 Hz) is observed on change of solvent. The pyridinium salt **19** has a $^1J_{^1H,^{13}C} = 180$ Hz, as expected for an sp^2-carbon atom.

c) The magnitude of the downfield shifts correlates qualitatively with the basicity of the thiolates. Ionization of the appropriate addition products of **19** is observed for 4-nitrothiophenolate, whereas the benzylthiolate addition product with **19** behaves like the phenylthiolate addition product **18**, except that the downfield shifts are smaller but increase in magnitude as the temperature is raised.

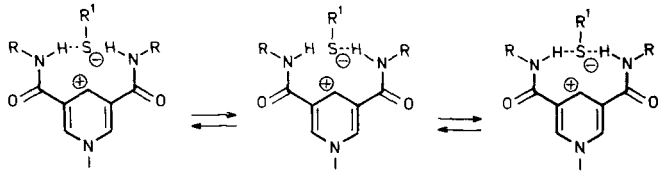
d) Isomerization to 1,2-substituted systems is not involved.

e) This analomous behavior is found only when the amide functionalities bear a proton. This is illustrated, for example, with **20a**, which ionizes virtually instantaneously and completely to the pyridinium thiolate **20b** when dissolved in CD_3OD or other polar solvents.



f) The NMR observations are corroborated by the UV spectra, which are consistent with formation in polar solvents of an intermediate other than the pyridinium salt.

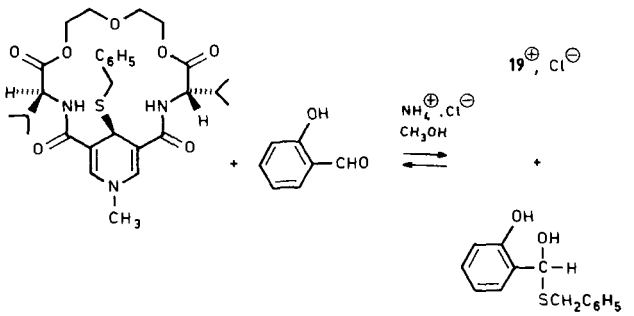
These observations bear an obvious resemblance to the seminal work of *Wallenfels* et al.[23a], some thirty years ago, on a variety of pyridinium salt/nucleophilic addition products. *Wallenfels* did not have available for his work the powerful tool of NMR spectroscopy.



21a **21b** **21c**

We have suggested[27] that our observations can be accommodated by an intermediate having the general structure **21a**–**c**. The complete solvolytic cleavage of the thiolate in polar, mildly nucleophilic solvents is prevented by hydrogen bonding to the amide proton (actually, deuterium under the reaction conditions). The exact hybridization of C-4 in **21** is currently an open question. We view **21**, in fact, as an intimate ion pair in the sense defined by *Sneen*[28]. Our observations are doubtless related to the elegant work on other pyridinium salt ion pairs carried out previously by *Steglich* and *Höfle*[29].

Returning to possible implications for 3-phosphoglyceraldehyde dehydrogenase[30], we have shown that the reversible reaction shown in Scheme 7 smoothly occurs in CH_3OH, but not in $CHCl_3$. This is completely analogous to the step necessary for the enzymic mechanism postulated in equation (c).



Scheme 7.

There remain many unanswered questions. For 3-phosphoglyceraldehyde dehydrogenase, the validity or not of our mechanistic suggestion can be established only with the aid of appropriate biochemical experiments. A special role is played by the carboxamides in **21**, namely hydrogen bonding. One may speculate that in $NAD^{\oplus}$/NADH similar hydrogen bonding effects might be important, a surmise already made in a different context by *Buck* and *Donkersloot*[31] on the basis of ab initio calculations. In particular, the conformation of the carboxamide group with respect to the ring could become a factor governing reactivity. Other unanswered questions have to do with the exact structure of **21**. Is it truly an ion pair with non-covalent bonding of the pyridinium and thiolate ions or is some type of "stretched" carbon-sulfur bonding involved? And exactly how does **21** (but not the covalent precursor) manage to transfer thiolate? We suspect that again some general, but not broadly recognized, principles are involved; we hope in time to define these better.

4. Transfer of Other Nucleophiles

In the course of our investigations of the chemistry described in the previous section, it occurred to us that one might also be able to use these chiral, bridged pyridinium salts as templates on which to carry out enantioselective aldol condensations[32]. This is illustrated in general terms in Figure 8. The enolate of **23** is expected to leave readily in

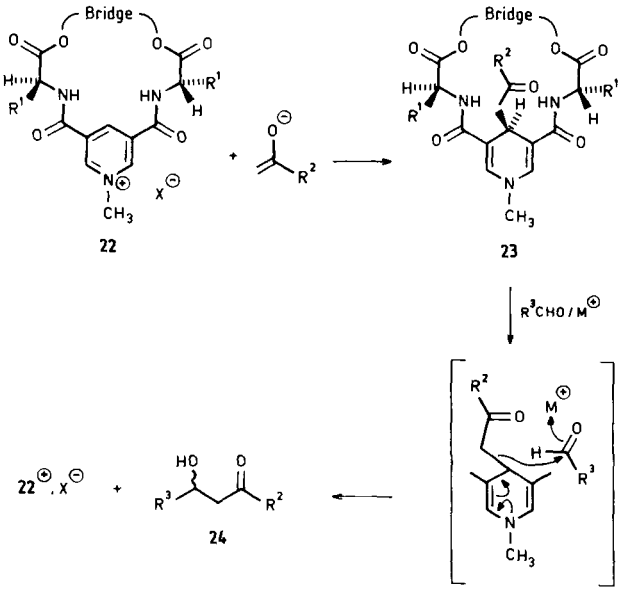
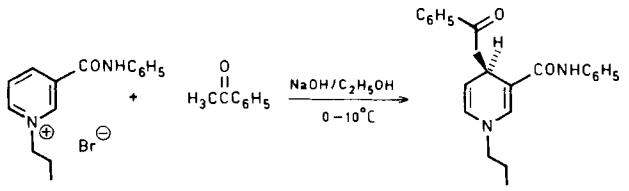


Fig. 8. Schematic mechanism for the aldol condensation using **22** as matrix.

the presence of an electrophile such as $SnCl_4$, $Mg(ClO_4)_2$, or $BF_3 \cdot O(C_2H_5)_2$, producing the aromatic pyridinium salt **22**. Some assumptions are, however, associated with this mechanism. The most important of these are a) that regioselective addition of enolates or their equivalents to **22** is possible and b) that the aldol condensation occurs on the chiral surface of the macrocycle rather then via an achiral metal enolate that has completely left **23**. The question of ion pairing as discussed in the previous section might also play an important role here.

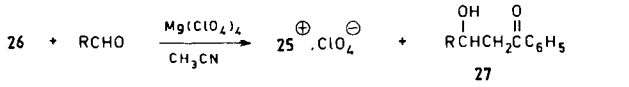
Adequate precedent exists for the addition of enolates to pyridinium salts[23j-o,33] and, moreover, an unusual precedent for the transformations outlined in Figure 8 has been described by *Steglich* and *Höfle*[23m,34]. We first established that enolate transfer as delineated in Figure 8 could be ac-

complished in a reasonably general fashion using a racemic enolate-pyridinium salt adduct. From **25** the adduct **26** could be prepared in good yield and in high regioselectivity. In CH_3CN at room temperature in the presence of a



25 **26**

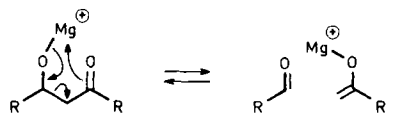
stoichiometric amount of $Mg(ClO_4)_2 \cdot 1.5\,H_2O$, condensation occurs smoothly to produce aldols **27** in 37—90% yield[35].



27

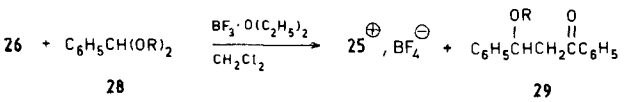
a, $R = C_6H_5$ (78–85%); b, $R = 2\text{-}CH_3OC_6H_4$ (85%); c, 2-furyl (90%); d, $(CH_3)_3C$ (47%); e, *trans*-$C_6H_5CH{=}CH_2$ (67%); f, $2\text{-}HOC_6H_5$ (37%)

Although these results are encouraging in that the desired reaction took place, two problems arise. Firstly, the addition of enolates to other pyridinium salts, especially those of general structure **22** shown in Figure 8, were not particularly regioselective; appreciable amounts of 1,2-adducts are formed. This is, of course, not too surprising; the addition tends to become more charge-controlled with harder nucleophiles, e.g. C nucleophiles which attack the more electron deficient 2-position[22,36]. Softer S-nucleophiles attack, within the detection limits of NMR spectroscopy, exclusively the 4-position. Secondly, under the conditions used here the aldol condensation is reversible; in other words, any transfer of chirality from a derivative of **23** is lost (Scheme 8)[37].



Scheme 8.

We have yet to provide a satisfactory solution to the problem of regioselectivity. The difficulty associated with reversibility is more easily attacked by changing the enolate acceptor from a carbonyl to an acetal group. This is, in essence, a variation of a method developed by *Mukaiyama* et al.[38]. For example, **26** condenses smoothly with the dimethyl acetal **28a** or diacetoxy derivative of benzaldehyde **28b**. Use of **28b** and related 1,1-diacetates leads under irreversible conditions to acylated aldols; the acetyl protect-

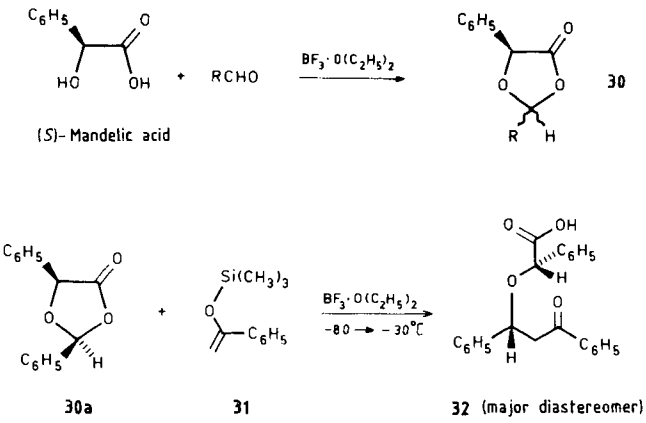


28 **29**

a, $R = CH_3$; b, $R = COCH_3$

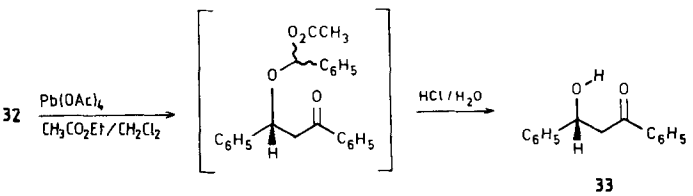
ing group can be subsequently removed with ease. This is not the case for **29a** and other methyl ethers. However, this method has yet to be applied successfully to the bridged chiral systems due to complications arising from the aforementioned problems of the regioselectivity of the addition.

One aspect may nevertheless be briefly mentioned. The ease with which the diacetoxy derivatives of benzaldehyde **28b** react with **26** led us to investigate the chemistry of compounds of the type **30**, prepared by condensation of the appropriate mandelic acid ((*S*)-enantiomer illustrated) with an aldehyde (or ketone) in the presence of $BF_3 \cdot O(C_2H_5)_2$[39]. For conformational reasons, the *cis*-isomers of **30** are the most stable[40] and can usually be isolated quite easily. Under the conditions developed by *Mukaiyama* et al.[38a], **30a** condenses with **31** in 98% yield to form a 93.5:6.5 mixture of diastereomers **32**. In other



(*S*)-Mandelic acid **30** **30a** **31** **32** (major diastereomer)

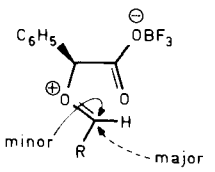
words, the more reactive carboxy group functions selectively as the leaving group under the reaction conditions. The major diastereomer of **32** is readily isolated pure by flash chromatography. The mandelate functionality is then removed by oxidative decarboxylation and hydrolysis to produce optically pure **33**[41].



33

This approach has been used with the trimethylsilyl enol ether of isobutyraldehyde and trimethylallylsilane as well

as the 1,3-dioxolan-4-ones **30** of 2-furaldehyde, acetophenone, propionaldehyde, and isobutyraldehyde. Good diastereomeric excesses are obtained, and, since both enantiomers of mandelic acid are commercially available, either enantiomer of the desired product is obtainable. The ste-



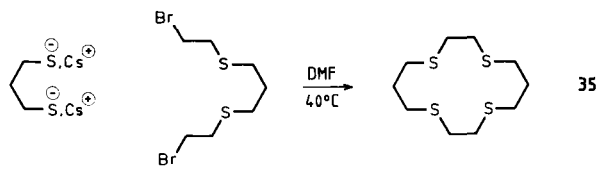
34

reochemistries of the major diastereomers formed on condensation can all be accounted for by assuming that **34** is a common intermediate which is attacked preferentially *trans* to the phenyl group of the mandelic acid. If this is the case, the initial stereochemistry of **30** should not be reflected in the condensation product. This is essentially what is found experimentally (and indeed *cis,trans*-isomers equilibrate under the experimental conditions). This has the consequence that the *cis,trans*-mixture of **30** formed initially can be used without prior separation[42].

5. Macrocycles as Chiral Ligands for Transition Metal-Catalyzed Reactions

One problem which has concerned us greatly is the "turnover" number with macrocycles. In other words, how does one prepare a macrocycle that regenerates itself after each reaction cycle? The answer, clearly, depends on the reaction[43]. The problem does not arise if the reaction concerned is intrinsically catalytic. Such a situation is encountered in the synthetically enormously interesting area of transition-metal catalyzed CC bond forming reactions[44].

We became interested in reactions of this type as the result of our finding that using the cesium salt method described in Section 2 we could also prepare macrocyclic sulfides[45]. The value of the method is illustrated by the fact that the yield of **35**, of interest as a ligand for copper ions, is only 7.5% following the approach in Scheme 9, but with $K^{\oplus}$ as counterion (in ethanol)[46]; however, **35** is produced routinely in 75—80% yield using $Cs^{\oplus}$[45,47].

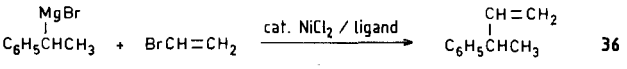


35

Scheme 9.

Cesium salts have also been used with success by several other groups for the synthesis of various macrocycles[48]; moreover, solutions of cesium salts in dimethylformamide (DMF) or dimethyl sulfoxide (DMSO) seem, in general, to have high nucleophilicities, which fact has been used to introduce oxygen[49] or sulfur[50] functionalities with clean inversion of configuration at centers prone to racemization or elimination. The various applications of cesium salts have recently been reviewed by *Vögtle* et al.[51,52].

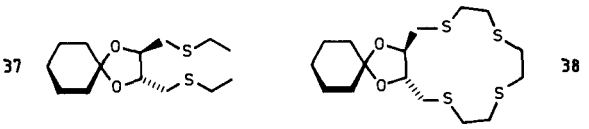
Sulfides have a firmly established reputation as poisons for various transition metal-catalysts. We judged it wise to first check whether simple macrocyclic ligands containing sulfur are compatible with a reaction involving transition metal-catalyzed bond formation. As model reaction, we selected the synthesis of 3-phenyl-1-butene **36**, which has been studied in great detail by *Consiglio* et al.[53] and *Kumada* et al.[54].



36

The nickel dichloride is solubilized with the aid of a ligand such as 1,2-di(diphenylphosphino)ethane. The catalytic cycle is believed to involve a Ni^0 intermediate which undergoes oxidative addition of vinyl bromide; ligand exchange with the Grignard reagent, followed by reductive elimination provides the coupling product **36**. Although its synthetic scope is still limited, this reaction is well suited for examining effects caused by changing the structure of the solubilizing ligands. With chiral phosphanes as ligands, enantiomeric excesses of up to 83% have been attained in this reaction[54b].

We were encouraged to find that racemic **36** was produced nearly quantitatively with 0.5% $NiCl_2$ and an equivalent amount of achiral **35**. This clearly indicates that the sulfide **35** does not poison the coupling reaction, but rather functions as an efficient ligand. Chiral sulfides **37** and **38** are readily available from (*S,S*)-tartaric acid. The macrocycle is synthesized with the aid of the cesium salt method. The coupling reaction proceeds rather sluggishly in the presence of **37** to provide virtually racemic **36** in 53% yield. On the other hand, cyclic **38** is an efficient li-



37 **38**

gand which in the presence of a catalytic amount of $NiCl_2$ smoothly induces formation of **36** in quantitative yield and a modest enantiomeric excess of 17%[55]. Recently, a series of macrocyclic sulfides made chiral by the inclusion of amino acids have been prepared and used in the synthesis of **36**; enantiomeric excesses of around 50% have been obtained with these ligands, whose design is steadily improving and which are currently being applied to other enantioselective CC bond forming reactions[56].

6. Perspectives

In this article, I have described organic and organometallic chemistry in which macrocycles play a central role. Such macrocycles can be prepared on a routine basis in

gram quantities with the investment of a few days work. This does not make them commonly used reagents, but it does mean that it is now feasible to perform chemistry with them; not so long ago their difficult syntheses condemned most macrocycles to the realm of chemical curiosities. Nevertheless, it is advantageous to work catalytically for the pragmatic reason of reaping a greater return for the synthetic effort invested. Hence, our interest in transition metal-catalyzed reactions.

The macrocycles described here are certainly not enzymes, but sometimes they carry out functions reminiscent of enzymes—enantioselective reductions and catalytic formation of CC bonds are good examples—but under abiotic conditions. This is an advantage, since the full power of chemical synthesis can be brought to bear without having to deal either with the limitations of water as a solvent or the usual restrictions of temperature.

Perhaps in the long run the use of macrocycles will not prove to be the best alternative to enzymes. On the one hand, they present the opportunity of introducing functional groups according to a pre-designed plan; on the other hand, some of the best systems so far found, for example, catalytic asymmetric synthesis, depend to a great extent on self organization of the reactants. One might mention the Sharpless[57] method for epoxidation of allylic alcohols, alkaloid-catalyzed Michael additions as studied by *Hiemstra* and *Wynberg*[58], enolate alkylations[58], and rhodium-catalyzed hydrogenations of α,β-unsaturated amino acids as developed by *Knowles* et al.[60] inter alia[61]. Moreover, the ability of molecules to orient themselves spontaneously is rarely illustrated so clearly as by micelles and vesicles; some of the aspects of this type of chemistry have recently been discussed by *Fendler*[62].

I think that the task of preparing an "artificial enzyme", i.e. a synthetic molecule that replaces the function of a natural enzyme in all respects, is well-nigh impossible (and not even especially desirable) using the approaches described here. The peptide structure plays too great a role in enzymes. It is certainly difficult to envisage how one could mimic, for example, the effects of the local dipole formed by the α-helix extending from the active site in a thiol protease such as papain[63], short of synthesizing the peptide section and attaching it with the proper orientation to the synthetic enzyme. This structural aspect has virtually inimitable consequences for the active site. On the other hand, the totally different approach to the rational design and synthesis of peptides discussed by *Kaiser* and *Kézdy*[64], should allow one, at least in principle, to reconstruct (a better word than "mimic", here) such special structural features.

Chemists are learning how to design molecules to carry out particular tasks for them. As knowledge about biological structures increases, the combination of this architectural insight with the not inconsiderable powers of mechanism and synthesis developed in the last decades will open roads to new understanding. The problem, as always, will be the proper application of the information gained.

A considerable part of this review is based on sections of the doctoral theses of J. G. de Vries (1979), C. B. Troostwijk (1981), B. J. van Keulen (1984), and A. G. Talma (1984). The very special contributions over the years by J. Buter, W. H. Kruizinga, S. H. Mashraqui, M. Lemaire, P. Jouin, B. K. Vriesema, and T. J. van Bergen must also be mentioned. I have been priviliged to have these and other talented coworkers mentioned in the references. Present-day chemistry is a question of cooperation among many people; my thanks indeed to all those, who with so much good will, dedication, and enthusiasm, have made this cooperation a reality.

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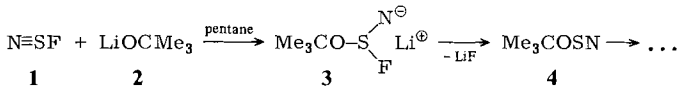
Conversion of "LiNS(F)OCMe$_3$" into an (Li$_8$)$_2$ Double Cluster**

By *Wilhelm Isenberg, Rüdiger Mews**, and *George M. Sheldrick*

Nucleophilic substitutions at thiazyl fluoride **1**[1] should open up access to thiazyl derivatives R–S≡N. Members of this class of compounds are, however, only stable in a few cases; in many instances, complex secondary reactions are observed[2]. Addition of the nucleophile **2** to **1** is expected



1 **2** **3** **4**

to be the initial step in a substitution of this type; cleavage of LiF and additional reactions follow whose products have not yet been identified. Alternatively, **3** is converted into the more stable mixed salt of composition **5**[3]:

$\{Li_8[Me_3COS(N)F]_4F_2\}[Li_4(OCMe_3)_5]_2 \cdot 4C_5H_{12}$ **5**

When less than the stoichiometric amount of **1** is used, LiF is only partially eliminated and some **3** is obtained. In the formation of **5**, four moieties of **3** combine with four additional $Li^{\oplus}$ to give two "$Li_4(N/F)_4$ eight-membered rings" linked by four Me_3CO–S bridges; an $F^{\ominus}$ ion is located over the midpoints of the respective rings (Fig. 1)[5]. F and N atoms are distributed statistically over the puckered, eight-membered rings. Formally, a section of this type has the charge +2 and is neutralized by two $[Li_4(OCMe_3)_5]^{\ominus}$ fragments which enclose the central eight-membered rings. It cannot be stated whether the $[Li_4(OCMe_3)_5]^{\ominus}$ moiety is a section from the structure of the educt $LiOCMe_3$, since its structure is unknown[4].

In reactions of organolithium compounds and lithium amides in which lithium halides are formed, self-inhibition frequently arises[6,7] due to formation of complexes between the educts and lithium halides. Intermediates can also be stabilized by formation of "mixed compounds" such as **5** (mixed salts of lithium and fluoride, alkoxide, and imide).

5 is of considerable interest not only for NSF chemistry, but also for the chemistry of Li. Previously, numerous lithium clusters have been described which consist of Li_nR_n moieties with n = 4[7–13], 5[14], and 6[15–17] (R = organo[7,8,11,13,16], O-[12], N-[9,10,14,15], Si-residues[17], as well as halogen[7,9,11]). From this point of view, **5** can be considered as arising from the linkage of two $Li_8(OCMe_3)_5F$ clusters (Fig. 1) by four anions of **3**, which act as bridges. The eight lithium atoms form a tetragonal antiprism; the distances of the inner Li′ atoms, which are bridged by F or N, are 264–270, those of the outer, O-bridged Li″ atoms are 233–243, and the distances Li′–Li″ are between 275 and 280 pm. Bond lengths of a similar order of magnitude are found also in smaller clusters. The triangular faces of the antiprism are bridged by four Me_3CO groups (O–Li″ 188.3, O–Li′ 190.1 pm), and the outer quadrangular face is capped by an additional moiety of this type (O–Li″ 199.1 pm). The fluorine ligand which bridges the inner quadrangular face lies within the antiprism and, hence, F interacts with all the lithium atoms (Li′–F 198.5, Li″–F 246.4 pm); in this way it probably contributes towards the stabilization of the cluster (Fig. 1).

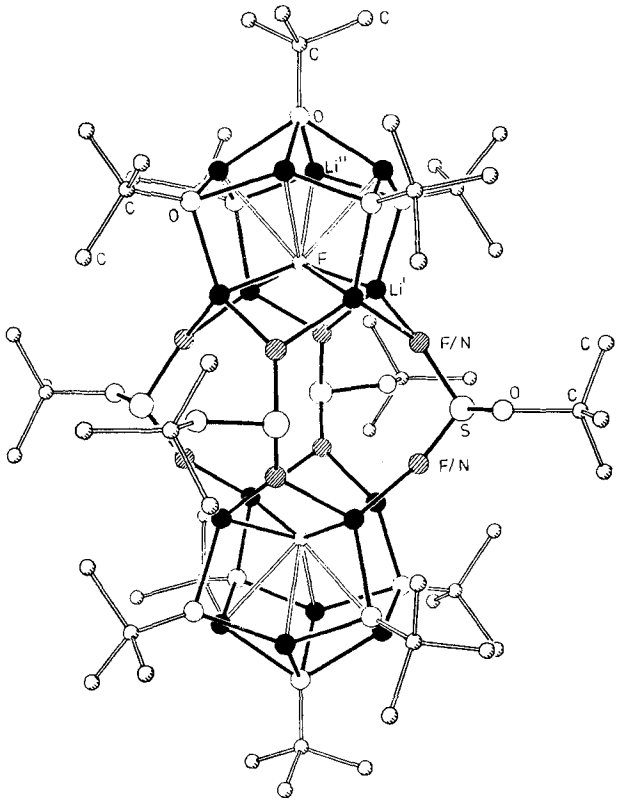


Fig. 1. Structure of **5** in the crystal (without hydrogen atoms, solvent, and second orientations of disordered *tert*-butyl groups).

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1, 18820-63-8; **2**, 1907-33-1; **3**, 92240-97-6

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[1] Review: O. Glemser, R. Mews, *Angew. Chem.* 92 (1980) 904; *Angew. Chem. Int. Ed. Engl.* 19 (1980) 883.
[2] W. Isenberg, Dissertation, Universität Göttingen 1984.

[3] 1 (10.9 mmol) in a stream of dry N_2 is passed into a stirred solution of $LiOCMe_3$ (30.5 mmol) in 40 mL *n*-pentane at −60 °C. The coolant is removed and the mixture gently warmed up to room temperature and stirred for 12 h. The solvent is then carefully removed, resulting in formation of a yellow, glass-like solid, which is taken up in *n*-pentane and cooled to −35 °C. The solvent is slowly removed at this temperature. Crystals of **5**, which can be separated manually, are included in the residual solid. **5** decomposes immediately at room temperature in vacuo, but under N_2 is stable for a few hours. If they are imbedded into KelF wax, the crystals can be stored for several weeks.
[4] $LiOCMe_3$: Space group C2, Cm or C2/m, $a=2963$, $b=1767$, $c=1032$ pm; $\beta=93°$: K. Huml, *Czech. J. Phys. B 15* (1965) 699.
[5] Siemens AED-2 single crystal diffractometer, $Mo_{K\alpha}$ radiation, computer: Data General Eclipse S-250, all programs from *G.M.S.* **5**, space group C2/m, $a=2263.7(3)$, $b=1938.6(4)$, $c=1329.1(2)$ pm; $\beta=124.83(1)°$, $V=4.783\times10^9$ pm^3; 1933 independent reflections with $F>3\sigma(F)$; $R=0.167$, $R_w=0.136$, $w^{-1}=\sigma^2(F_0)+0.001|F_0|^2$, $\rho_{calc.}=1.19$ g/cm^3. Further details of the crystal structure investigation can be obtained from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, by quoting the depository number CSD 51065, the names of the authors, and the journal citation.
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Asymmetric Microsomal Epoxidation of Simple Prochiral Olefins**

By *Volker Schurig** and *Dorothee Wistuba*

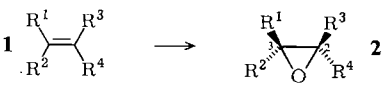
As highly selective catalysts, enzymes can distinguish not only between enantiotopic groups and faces of prochiral molecules *(product enantioselectivity)* but also between the enantiomers of racemic mixtures *(substrate enantioselectivity)*[1].

In the metabolism of xenobiotics having aromatic or olefinic double bonds in the endoplasmic reticulum of liver cells, reactive oxiranes (epoxides) are formed enantioselectively. Thus, cytochrome P-450 dependent monooxygenases epoxidize aromatic polycyclic hydrocarbons with high enantioselectivity[2]. The asymmetric epoxidation of prochiral olefins (styrene, 1-octene) is also known[3]. The reactive oxiranes formed often exhibit a high mutagenic and carcinogenic potential which frequently depends on the enantiomer composition and the absolute configuration[4]. Until now, the methods used to determine the enantiomeric purity in studies of enantioselective epoxidations have been time consuming and imprecise[5].

We have found that in microsomal epoxidations monooxygenases can differentiate between the enantiotopic faces of the double bond of small, aliphatic, nonfunctionalized, prochiral olefins **1**; the extent of product enantioselectivity is found to depend critically on the structure of the olefin. In order to determine rapidly and precisely the enantiomeric excess and absolute configuration of the oxiranes **2** formed, complexation gas chromatography was used[6]. By means of this method, even highly volatile oxiranes which are difficult to isolate can be analyzed reliably on the nanogram scale by head-space analysis of incubation mixtures without recourse to derivatization procedures. In this way, the enantioselective conversion can be monitored continuously without requiring to interrupt the reaction; this is a prerequisite for distinguishing between product and substrate selectivity.

We studied the product enantioselectivity of the enzyme-catalyzed aerobic epoxidation of prochiral olefins **1** to oxiranes **2** by liver microsomes of male, phenobarbital-induced Wistar rats. The results are summarized in Table 1[7]. Figure 1 shows a representative complexation gas chromatogram.

Table 1. Microsomal enantioselective epoxidation of simple olefins [7]. The formula refers to the enantiomers of (2*R*)-configuration (**2e**: (3*R*)-configuration.



	R^1	R^2	R^3	R^4	Enantiomer ratio [a]	*e.e.* [%] [b]
a	H	H	Me	H	30 (*R*) : 70 (*S*)	40 ± 1.4 [c]
b	H	H	Et	H	30 (*R*) : 70 (*S*)	40 ± 1.0
c	H	H	$HC=CH_2$	H	30 (*R*) : 70 (*S*)	40 ± 1.4
d	H	Me	Me	H	43 (2*R*,3*R*) : 57 (2*S*,3*S*)	14 ± 1.0
e	H	Me	Me	Me	0 : 0	0
f	H	H	Et	Me	39 (*R*) : 61 (*S*)	22 ± 4.0
g	H	Me	Et	H	48 (2*R*,3*R*) : 52 (2*S*,3*S*)	4 ± 1.2
h	Me	H	Et	H	48 (2*R*,3*S*) : 52 (2*S*,3*R*)	4 ± 1.1

[a] Absolute configurations were determined by coinjecting oxiranes of known chirality (K. Hintzer, dissertation, Universität Tübingen 1983). The absolute configuration of vinyloxirane **2c** was assigned using the "quadrant rule" [6]. [b] The error limits refer to the reproducibility of a minimum of seven incubations with one microsome preparation. [c] When racemic methyloxirane **2a** was incubated with 2-(trichloromethyl)oxirane-inhibited microsomes the *e.e.* did not change by 0 ± 1% in the gas phase. This therefore ensures that the *e.e.* values determined by complexation gas chromatography are not altered by enantioselective associations in the incubation medium (e.g. by chiral cell membranes).

The highest enantioselectivity of the cytochrome P-450 dependent monooxygenases was observed in the epoxidation of olefins with terminal double bonds (**1a**, **b**, **c**, **f**). Neither extension of the length of the carbon chain nor alteration of its degree of hybridization has an effect on the enantiomeric composition. In contrast, the enantioselectivity of the enzyme system is markedly influenced by the degree of substitution of the olefinic double bond. Thus, the enantiomeric excess decreases noticeably along the series methyloxirane **2a** > *trans*-2,3-dimethyloxirane **2d** > trimethyloxirane **2e** (= zero). The (*S*)-enantiomer is always formed preferably. The molecular geometry of the olefin **1** also influences the enantioselective behavior of monooxygenases. Comparison of the microsomal epoxidation of isomeric pentenes indicates that the enantiomeric excess is higher for the 2,2-disubstituted oxirane **2f** than for the *cis*/*trans*-2,3-disubstituted isomers **2h** and **2g**. These *cis*/*trans*-oxiranes exhibit only a slight (equal) enantiomeric excess.

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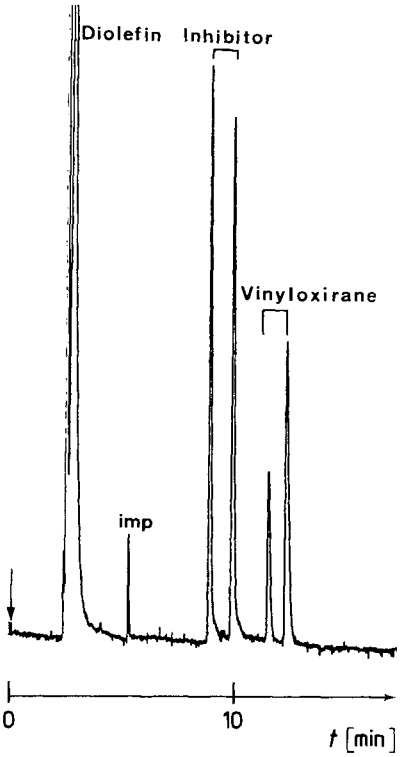

Fig. 1. Detection of the enantioselective microsomal epoxidation of 1,3-butadiene (="diolefin") **1c** to vinyloxirane **2e**. First enantiomeric pair: 2-(trichloromethyl)oxirane (inhibitor). Second enantiomeric pair: vinyloxirane (*e.e.*: 40% (*S*)). Column: 40 m × 0.25 mm deactivated glass capillary coated with 0.125 *m* nickel bis(3-heptafluorobutyryl-(1*R*)-camphorate) [6] in OV 101. 70°C, 2 bar N_2. imp. = impurity.

The oxiranes **2** occur in "steady-state" concentrations since they are hydrolyzed to diols by the epoxide hydrolase present in the microsomal fraction. The continuous determination of the enantiomeric composition of the oxiranes indicates that this secondary reaction also proceeds asymmetrically ("kinetic resolution"). In **2a**—**h** the (*S*)-enantiomer reacts more rapidly than the (*R*)-enantiomer[8]. Informative data with respect to the product enantioselectivity of the oxirane can therefore be obtained only by effective inhibition of the epoxide hydrolase[9]. For this purpose, 2-(trichloromethyl)oxirane has been used as an inhibitor. In the complexation gas chromatogram, the enantiomers of the inhibitor are eluted before the oxiranes **2a**—**h** (cf. also Fig. 1). If the enantiomer composition of the oxiranes formed is determined by complexation gas chromatography as a function of the incubation time, a constant value is found (enantioselective formation reaction) provided the inhibitor is present in excess; thereafter, hydrolysis (enantioselective reaction) of the oxiranes commences. These results underline the necessity of continuously monitoring both the enantiomeric excess and the concentration of the oxirane during incubation. The method of complexation gas chromatography used here for the first time has therefore proved to be a reliable probe for the investigation of asymmetric enzymatic reactions.

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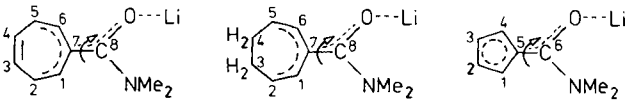
[5] The enantiomeric purity is given as enantiomeric excess *e.e.* [*e.e.* = 100 ([*S*]−[*R*])/([*S*]+[*R*])].
[6] V. Schurig, W. Bürkle, *J. Am. Chem. Soc. 104* (1982) 7573; V. Schurig in J. D. Morrison: *Asymmetric Synthesis. Vol. 1*, Academic Press, New York 1983, p. 59.
[7] The incubation mixture of 0.5 mL total volume contains microsomes (1.5 mg protein/mL), 0.15 M phosphate buffer pH 7.4, NADP® (10^{-3} M), isocitrate dehydrogenase (0.1 I.U.), (±)-isocitrate (8×10^{-3} M), 2-(trichloromethyl)oxirane (4×10^{-3}–9×10^{-3} M), $MgCl_2$ (5×10^{-3} M) and olefin **1** (3–13 μmol). Temperature: 37°C. Incubation time: 30 min.
[8] The racemic oxiranes are incubated with microsomes (1.5 mg protein/mL) in 0.15 M phosphate buffer (pH 7.4) at 37°C; the enzymatic hydrolysis is studied by complexation gas chromatography. The incubation time (maximum 2 h) is a function of the substrate.
[9] If, for example, in the microsomal epoxidation of 1,3-butadiene to vinyloxirane the inhibition of the epoxide hydrolase is omitted, a racemic product is feigned when both formation and hydrolysis of the (*S*)-enantiomer are preferred; H. M. Bolt, G. Schmiedel, J. G. Filser, H. P. Rolzhäuser, K. Lieser, D. Wistuba, V. Schurig, *J. Cancer Res. Clin. Oncol. 106* (1983) 112.

Easy Rotation about the Exocyclic Carbon-Carbon Bond in Lithium α-Aminoenolates: A Comparison**

By *Gernot Boche**, *Ferdinand Bosold*, and *Robert Eiben*

In the α-aminoenolates ("amide enolates") **1**, **2**, and **3** we found for the first time an easy rotation about the exocyclic CC double bond[1] in a compound of this sort.



1 **2** **3**

The 100-MHz ^{1}H-NMR spectra of lithium dimethylamino(cycloheptatrienylidene) methoxide **1** are temperature-dependent[2]. At 39°C, the signals of H^1 and H^6 ($\delta = 5.17$ and 4.93; an assignment was not made) are noticeably separated, whereas at 70°C they coalesce due to rapid rotation about the C^7C^8 bond, and at 83°C split into a doublet.

A free activation enthalpy of $\Delta G^+(70°C) = 17.5 \pm 0.5$ kcal/mol is calculated for the barrier to rotation in **1**. The barrier for rotation about C^7C^8 in the dihydro analogue **2** was determined in a similar way (ΔG^+ (25°C) 14.0 ± 0.5 kcal/mol). The rotation about C^5C^6 in **3**, on the other hand, could not be frozen-in even at −106°C, i.e. $\Delta G^+(-106°C) < 8$ kcal/mol[3,4].

In **2**, the negative charge is stabilized in the cross-conjugated pentadienide moiety, in **3**, in the cyclopentadienide moiety. The energetic advantage of the cyclic 6π-delocalization ("aromaticity") in **3** explains the low barrier to ro-

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tation in **3** ($\Delta\Delta G^{+} > 6$ kcal/mol). 8π-"Antiaromaticity" in the cycloheptatrienide ion, on the other hand, cannot be of much significance *energetically*, since the difference in barriers for **1** and **2** is only 3.5 kcal/mol. According to the X-ray structure analysis, **1**·2THF has a "pentadienide ion" structure (long C^2C^3 and C^4C^5 bonds and a short C^3C^4 bond)[4]. Likewise, MO calculations on diverse cycloheptatrienyl anions lead to similar structures[5], which is in accordance with the small $\Delta\Delta G^{+}$ value for **1** and **2**. At the same time, cycloheptatrienide ion derivatives show paratropic shifts of the signals in the ^{1}H-NMR spectrum[2b,6].

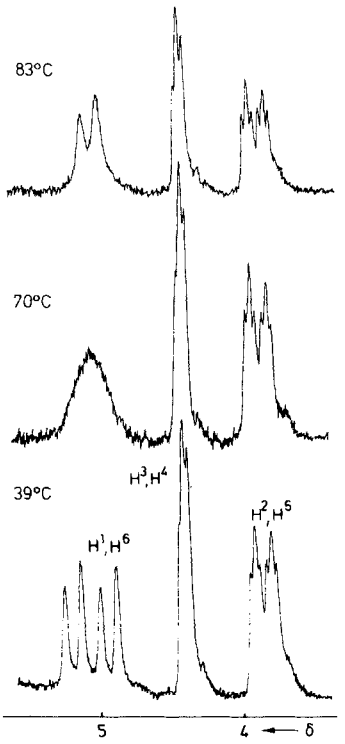

Fig. 1. ^{1}H-NMR spectra (100 MHz) of **1** in [D_8]tetrahydrofuran (THF) at 83, 70, and 39°C.

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CAS Registry numbers:
1, 86233-66-1; **2**, 92270-11-6; **3**, 92270-12-7

[1] Lithium 1-(dimethylamino)vinylate (lithium enolate of *N,N*-dimethylacetamide) e.g. is conformationally stable: R. P. Woodbury, M. W. Rathke, *J. Org. Chem. 42* (1977) 1688.

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[3] The conformation of lithium (cyclopentadienylidene)ethanolate (lithium enolate of the methyl ketone) is stable at 55°C (ΔG^{+}(55°C) > 18 kcal/mol, while the rotation about C5C6 in lithium cyclopentadienylidene(methoxy)methanolate (Li-enolate of the methyl ester) freezes in at −14°C (ΔG^{+}(−14°C) = 13.0 ± 0.2 kcal/mol): G. Boche, R. Eiben, W. Thiel, *Angew. Chem. 94* (1982) 703; *Angew. Chem. Int. Ed. Engl. 21* (1982) 688; *Angew. Chem. Suppl. 1982*, 1535; thus, this barrier depends considerably on the strength of the acceptor substituents.

[4] **3**: The rotation about C6–N in **3** is also of interest. A broadening of the *N*-methyl signal is first observable at −100°C, a splitting first at −106°C (ΔG^{+}(−106°C) ≈ 8 kcal/mol). The C6N bond should thus have considerably less double bond character than a normal "amide bond". This is consistent with bond lengths of ≈ 1.34 Å for CN in amides (W. E. Stewart, T. H. Siddall, III, *Chem. Rev. 70* (1970) 517); C8N in **1**·2THF: 1.435 Å. X-ray structure analysis of **1**·2THF, W. Bauer, T. Laube, D. Seebach, *Chem. Ber.*, in press. We thank Professor *Seebach* for a copy of the manuscript.

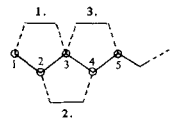
[5] a) M. J. S. Dewar, N. Trinajstic, *Tetrahedron 26* (1970) 4269; b) A. W. Zwaard, A. M. Brouwer, J. J. C. Mulder, *Recl. Trav. Chim. Pays-Bas 101* (1982) 137; c) A. W. Zwaard, Ph. D. Thesis, Universität Leiden 1983; d) W. Thiel, G. Boche, unpublished results; see also R. Breslow, *Acc. Chem. Res. 6* (1973) 393.

[6] See, e.g., S. W. Staley, A. W. Orvedal, *J. Am. Chem. Soc. 95* (1973) 3382.

Iterative Cyclopentane Annulation of α,β-Enones**

By *Maria Dorsch, Volker Jäger**, and *Wolfgang Spönlein*

There is currently extensive interest in the synthesis of polycyclopentanoids[1], primarily because this structural moiety is present in a variety of biologically active natural products and theoretically interesting molecules. However, efficient protocol for *iterative* cyclopentane annulation is rare[1,2]. The following communication reports a four-step sequence of this kind, to convert substituted α,β-unsaturated carbonyl compounds into ring-homologous cyclopentenones. To-date, this has enabled the synthesis of several mono- and bicyclic enones, as well as a tricyclic derivative.

A 

The new annulation sequence is summarized by formula **A**. The key steps (see Scheme 1) are:

(1) Preparation of an allylic alcohol from an α,β-enone by $LiAlH_4$ reduction or Grignard addition;
(2) Claisen rearrangement of the allylic alcohol involving *Johnson*'s orthoester[3a,b] or *Ireland*'s ketene acetal modification[3b–d], followed by hydrolysis to 4-alkenoic acids[3e];
(3) Polyphosphoric acid (PPA)-induced cyclodehydration[1,4] to cyclopentenones, with appropriate C=C migration.

Some of the results are given in Table 1. The synthesis of the bicyclic enone **7c**[5a] (an intermediate in a synthesis of isocomene by *Paquette* et al.[1a]) serves as an example to illustrate both the principle and the details of this sequence: Reaction of methacrolein **1c** with ethylmagnesium bromide afforded 2-methyl-1-penten-3-ol **2c** in 88% yield, which with triethyl orthoacetate, at ca. 140°C, was transformed into the 4-methyl-4-heptenoate and subsequently hydrolyzed to **3c**. Heating **3c** in PPA led to the 2,3-dialkylcyclopentenone **4c**, which was isolated in 96% yield (GC purity: 97%). The allylic alcohol required for the second cycle was obtained cleanly and quantitatively by $LiAlH_4$ reduction.

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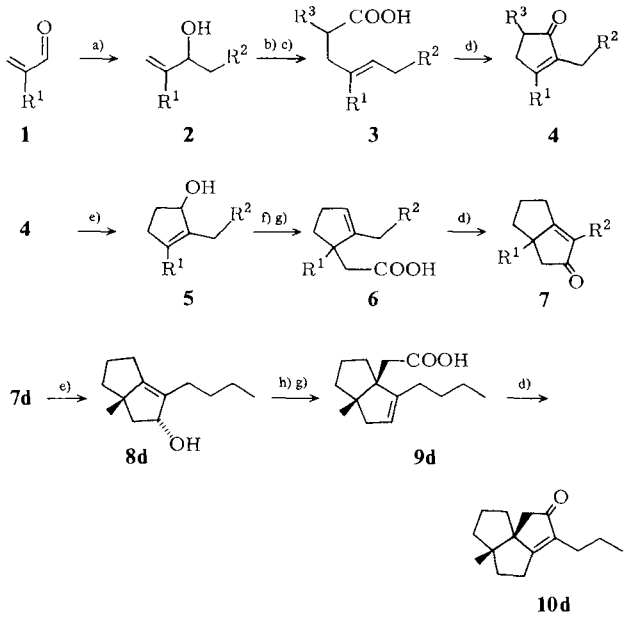
[**] We thank Dr. *E. Guntrum* and *M. Treiber* for carrying out some experiments. This work was supported by the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie, Bayer AG, BASF AG, Haarmann & Reimer GmbH, and Hoechst AG.



Scheme 1. Iterative cyclopentane annulations. a) R^2CH_2MgI, Et_2O, 0°C; dilute hydrochloric acid. b) $R^3CH_2C(OEt)_3$, EtCOOH, 135–140°C [3a]. c) KOH, MeOH–H_2O, reflux [3e]. d) PPA (ca. 83.5%, $n_D^{25} \approx 1.4721$ [7]); **7a**: 110°C/7 h; **7b**: 115°C/8 h; **7c**–**7e** 110°C/3 h. e) $LiAlH_4$, Et_2O, –10°C, for **5b**–**5e**; $LiAlH(OMe)_3$, tetrahydrofuran (THF), 0°C, 17 h for **5a**. f) Ac_2O, pyridine, 4-dimethylaminopyridine (DMAP) (cat.), room temperature. g) LICA, THF-hexamethylphosphoric triamide (HMPT), *t*BuSiMe$_2$Cl, –78→60°C; AcOH [3d]. h) AcOH, PPh_3, EtO_2C–N=N–CO_2Et, benzene, room temperature [6].

Table 1. Yields in the synthesis of monocyclic (1st cycle) and bicyclic (2nd cycle) enones according to Scheme 1.

	R^1	R^2	R^3	Yield [%] 1→4	4→7
a	H	H	H	24	4
b	CH_3	H	H	49	25
c	CH_3	CH_3	H	69	45
d	CH_3	*n*Bu	H	75	69
e	CH_3	*n*Bu	CH_3	67	— [a]

[a] Not investigated.

However, the reaction of cyclopentenols with orthoacetate either did not proceed as desired, or gave unsatisfactory yields, as checked with **5a**, **5b**, and **5d**. To overcome this difficulty, **5c** was acetylated (94%) and rearranged via the ketene acetal (formed by lithium cyclohexylisopropylamide (LICA)/*tert*-butyldimethylchlorosilane[3d]) to yield the cyclopentenylacetic acid **6c** (59%) containing *one quaternary center*. PPA cyclization proceeded smoothly and gave the bicyclo[3.3.0]octenone **7c** (82%). As anticipated, the *endo* double bond of **6c** first had been shifted into the *exo* position; the resulting isomer then had selectively been trapped from the mixture by acylium ion attack.

How many times can one repeat this sequence? In order to demonstrate the utility of this iterative process for a *third* cycle, **7d** was reduced by $LiAlH_4$ to the bicyclooctenol **8d**, with high stereoselectivity and in quantitative yield. However, contrary to expectation (Dreiding models) this turned out to be the *endo* alcohol (NOE difference measurements), unsuitable for the Claisen rearrangement to follow[5b].

Obtaining the wrong stereoisomer (*endo*) was of no serious consequence, since it was readily converted into the desired *exo* acetate via the azodicarboxylate method (*Mitsunobu*)[6] in 82% yield (ca. 80% purity according to ^{1}H- and ^{13}C-NMR). The *exo* acetate, obtained as above, was lithiated and silylated to afford the ketene acetal[3d], which after isolation was subjected to the rearrangement and gave the carboxylic acid **9d** containing *two vicinal quaternary centers* in 42% yield[3f]. Reaction of the latter with PPA, followed by MPLC purification of the crude product, furnished the tricycle **10d** in 60% yield, with an overall yield of 21% for the third cycle.

The additional entries in Table 1 demonstrate the potential of this synthetic scheme. For example, dihydrojasmone **4d**[4a,c] and the unnatural methyldihydrojasmone **4e** are now easily accessible on a 10g-scale. With less substituted substrates, the PPA cyclization proved to be unsatisfactory; e.g., 2-methylcyclopentenone was obtained in 32% yield from **3a**[4b]. The crucial step in the annulations is the Claisen-Ireland rearrangement which introduces the acetic acid side chain. The remaining steps all proceed in good to very good yield. Numerous applications of this methodology are conceivable, specifically when taking advantage of the PPA-induced C=C isomerization/cyclodehydration step.

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[5] a) All compounds gave correct elemental analyses and characteristic IR, ^{1}H-NMR, and ^{13}C-NMR data; b) a DIBAH reduction, suggested by a referee, afforded a mixture of **8d** (as main product) and, at most, small amounts of the *exo* isomer.

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[7] R. G. Downing, D. E. Pearson, *J. Am. Chem. Soc. 83* (1961) 1718.

Red α-Indium(III) Iodide**

By *Rüdiger Kniep** and *Peter Blees*

InI_3 is generally prepared from the elements, with subsequent purification by sublimation, and is obtained as yellow crystals. This yellow form of InI_3, namely β-InI_3, con-

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tains isolated In_2I_6 units each consisting of two $InI_2I_{2/2}$ tetrahedra linked via a common edge[1,2]. Prolonged storage at or below room temperature can lead—irreproducibly—to the transformation of individual domains of the yellow β-phase into a red α-phase; a concomitant change in the crystal structure has already been demonstrated by X-ray powder and Raman investigations[3,4]. A sample of the α-phase suitable enough for single crystal investigations cannot be obtained via this solid-solid transformation.

According to our differential thermoanalytical investigations, α-InI_3 transforms endothermically into the β-phase at +57 °C on heating ($\Delta H = 6.70$ kJ/mol). The transformation β→α is apparently kinetically inhibited; at +5 °C, however, β-InI_3 could be converted quantitatively into the α-phase within ca. three weeks.

Figure 1 shows the phase diagram of InI_3–$InBr_3$. Starting from InI_3, the InI_3–$InBr_3$ system has an extensive mixed-crystal phase, α-$InI_{3-x}Br_x$, adjacent to a two-phase domain between 184 and 194 °C in which α-mixed crystals ($x \cong 1$) are in equilibrium with an InI_3-rich melt. In this region it is possible to cultivate mixed crystals of the α-phase from the melt by cooling, albeit only in small yields. Information about the structures of the additional intermediary γ-, δ-, and ε-phases occurring at higher temperatures and increasing $InBr_3$ contents are not available[5]; $InBr_3$ crystallizes in the high-temperature $CrCl_3(YCl_3)$-type structure[6] with almost cubic close packing of the anions[7].

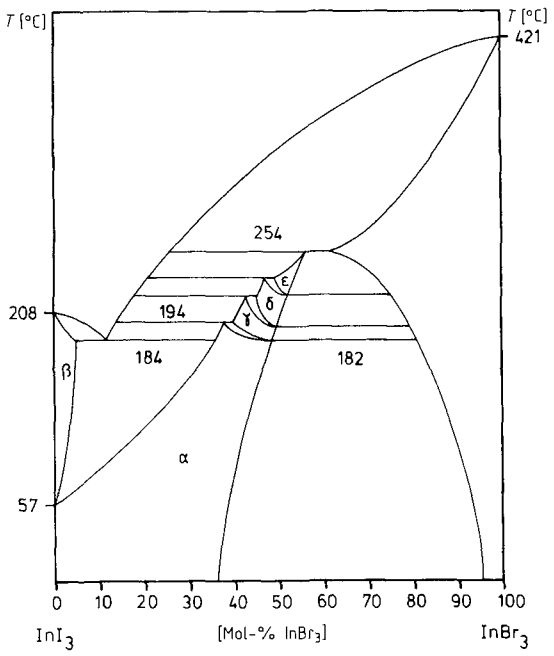

Fig. 1. Phase relationships at the quasi-binary section InI_3–$InBr_3$.

According to a crystal structure analysis[8] on a tabular pseudohexagonal single crystal of α-$InI_{3-x}Br_x$ ($x = 1$), the phase crystallizes in the low-temperature $CrCl_3$-type structure[9] with almost hexagonal close packing of the halogen atoms and ordered 2/3 occupation of the octahedral holes of every second octahedral layer by indium. The structural model was refined to convergence in the space groups R3 ($R = 0.046$) and $R\bar{3}$ ($R = 0.050$); according to the Hamilton significance test[10] the space group R3 is preferred with a probability of >99.5%. The temperature factors of the halogen positions also indicate negligible anisotropy by hexagonal treatment. For the "mixed atom" $I_{2/3}Br_{1/3}$, the atomic scattering factor of iodine[10] was applied with release of the occupation factor. Split positions, which would have taken into account the differences in the bond lengths In–I and In–Br, could not be consistently refined.

The lattice constants of α-InI_3 were ascertained by indexing the Guinier diagram ($a_{rh} = 8.011(5)$ Å, $\alpha = 53.64(4)°$; $a_{hex} = 7.229(1)$, $c_{hex} = 20.514(7)$ Å); α-InI_3 proves to have a substantially higher density (5.32 g/cm³) than β-InI_3 (4.70 g/cm³)[2].

Further examples of dimorphic aluminum, gallium, and indium trihalides have so far not been reported in the literature. However, in the framework of our current studies we recently found indications of $AlBr_3$ also being dimorphic: besides the known white modification (hexagonal close packing of the anions; isolated Al_2Br_6 units[11]) there exists a red modification, which crystallizes in flat hexagonal prisms.

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CAS Registry numbers:
InI_3, 13510-35-5; $InBr_3$, 13465-09-3

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[5] It cannot be ruled out that the γ-, δ-, and ε-phases may possibly be polytypic stacked variants in which, for the same octahedral coordination of indium, the transition from hexagonal close packed anions in α-InI_3 to cubic close packed anions in $InBr_3$ takes place.
[6] D. H. Templeton, G. F. Carter, *J. Phys. Chem. 58* (1954) 940.
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[8] Crystallographic data: α-InI_2Br: 567 (487) reflections, $R = 0.046$, R3; $a = 7.860(2)$ Å, $\alpha = 53.40(2)°$, $Z = 2$, $\rho_x = 5.14$ g/cm³ (hexagonal: $a = 7.063(2)$, $c = 20.158(5)$ Å; $Z = 6$). In–I/Br bond lengths 2.819(4)–2.876(4) Å. Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD 51003, the names of the authors, and the journal citation.
[9] B. Morosin, A. Narath, *J. Chem. Phys. 40* (1964) 1958.
[10] *International Tables for X-Ray Crystallography, Vol. IV*, Kynoch Press, Birmingham 1974.
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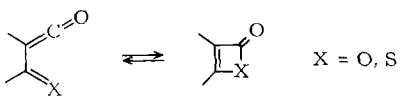
Acyl- and Thioacylketenes: Synthesis of 3-Benzoyl-4-phenylthiet-2-one**

By *Curt Wentrup**, *Hans-Wilhelm Winter*, *Gerhard Gross*, *Klaus-Peter Netsch*, *Gert Kollenz*, *Walter Ott*, and *Adolf G. Biedermann*

Little is known about four-membered unsaturated heterocycles, in general, and the possible acylketene (thioacylketene)/oxetone (thietone) valence tautomerization (**1** ⇌ **2**), in particular[1].



1 **2**

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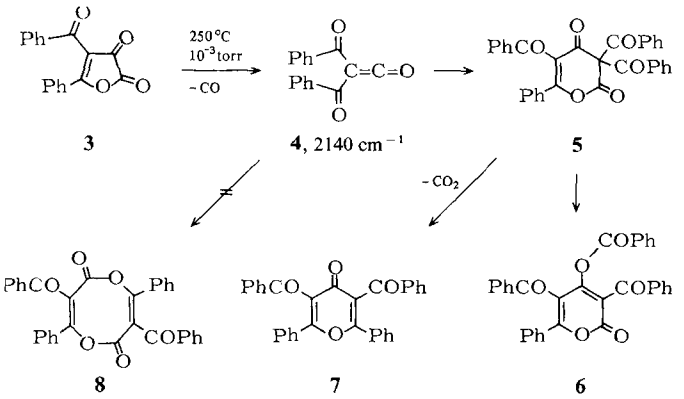
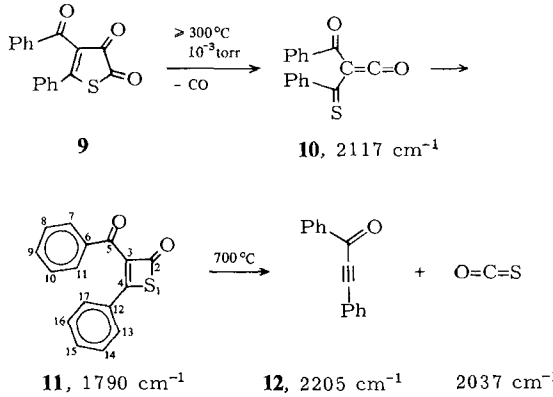
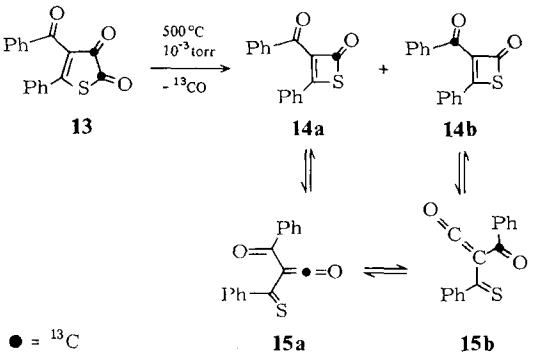
We have studied this problem using gas-phase pyrolysis of the furandione **3** and the thiophenedione **9** in conjunction with low-temperature spectroscopy. Pyrolysis of **3** at 250°C/10^{-3} torr resulted in CO extrusion and formation of the dibenzoylketene **4**, identified by a very strong absorption at 2140 cm^{-1} in its IR spectrum (−196°C) which disappeared on warming above −75°C. Attempts to obtain **4** on a preparative scale resulted in the isolation of a dimer **6** together with the γ-pyrone **7**. The formation of a dimer as well as **7** on decomposition of **3** in solution at 130°C has already been observed by *Ziegler* et al.[2], who assigned the structure **8** to the dimer. Since this would correspond to an unusual, if not impossible, [4+4]-cyclodimerization of dibenzoylketene **4**, the true nature of the dimer was established by X-ray crystallography and found to be **6**[3]. The formation of **6** is now readily understood in terms of a [2+4]-cyclodimerization of **4**, giving initially **5** which, under the experimental conditions (≥120°C) undergoes a 1,3-benzoyl shift to give **6**. There is precedence for thermal 1,3-benzoyl shifts in other systems[4].



The corresponding thiophenedione **9** is thermally more stable than **3** and at 300°C/10^{-3} torr decomposes only slightly, resulting in the appearance of a new band at 1790 cm^{-1} in the IR spectrum. At 500°C/10^{-3} torr, decomposition was complete, and the main product detected by IR spectroscopy (−196°C) absorbs at 1790, 1630, and 1515 cm^{-1}. A further, weak absorption at 2117 cm^{-1} is assigned to the ketene **10**. The "1790 cm^{-1}" and "2117 cm^{-1}" species both disappeared on warming above −40 and −80°C, respectively. On pyrolysis at higher temperatures (600—700°C), both the "1790 cm^{-1}" and the "2117 cm^{-1}" species disappeared, and new bands were observed at 2205 and 2037 cm^{-1} which arise from benzoyl(phenyl)acetylene **12** and OCS, respectively, as verified by isolation of the compounds (IR, MS, and GC).



Although the neat "1790 cm^{-1}" species oligomerizes, it was possible to obtain ^1H- and ^{13}C-NMR spectra of solutions of this compound in $CDCl_3$ at −40°C[5]. The ^1H-NMR spectrum is consistent with the presence of a phenyl and a benzoyl group. The ^{13}C-NMR chemical shifts and long-range couplings allow complete assignment as the thietone **11**. This is the first monocyclic thietone to be observed in solution. On the basis of the NMR spectra, the compound is virtually pure when formed from **9** at 500°C. At this temperature the decomposition products **12** and OCS do not form, and the ketene **10**, observable by IR spectroscopy, disappears at −80°C, presumably by cyclization to **11**.



The ^{13}C-NMR data for **11** are supported by increment calculations and by comparison with the only other completely characterized thietone, naphtho[2,3-*b*]thiet-2-one[1]. Nevertheless, in order to substantiate the chemical shift of the thietone carbonyl group in **11** ($\delta = 166.4$[5]), the doubly ^{13}C-labeled starting material **13** was prepared from 1,3-diphenyl-3-thiono-1-propanone) and [1,2-$^{13}C_2$]oxalyl chloride (90 atom-% ^{13}C). Pyrolysis of **13** at 500°C and examination of the product by IR spectroscopy (−196°C), mass spectrometry[6], and ^{13}C-NMR spectroscopy (−40°C) established that: 1) ^{13}CO had been eliminated, 2) the thietone **14** was labeled with one ^{13}C atom (90 atom-%), 3) *half* of this label was located on C-2 (**14a**), and 4) the other half was located in the carbonyl group of the benzoyl substituent (**14b**). In order to explain this unusual and unexpected result, we postulate that the thietone **14** interconverts with the ketene **15** in the gas-phase, *and* that the ketenes **15a** and **15b** undergo rapid interconversion by way of a 1,3-shift of a phenyl group. We have obtained proof for this novel reaction in a different system[7].

In conclusion, the diacylketene **4** does not appear to cyclize to an oxetone (**2**, X=O), but instead dimerizes. In contrast, the acyl(thioacyl)ketene **10** is thermodynamically less stable than the thietone **11**, to which it smoothly cyclizes. Nevertheless, an equilibrium **1** ⇌ **2** (X=S) prevails in the gas phase.

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3, 17571-17-4; **4**, 85601-40-7; **6**, 92314-63-1; **7**, 34959-15-4; **9**, 61350-68-3; **10**, 85601-41-8; **11**, 85601-42-9; **12**, 7338-94-5; **13**, 92314-64-2; **14a**, 92314-66-4; **14b**, 92314-67-5; PhC(S)CH_2C(O)Ph, 1215-43-6; Cl^{13}C(O)^{13}C(O)Cl, 92314-65-3.

[1] C. Wentrup, G. Gross, *Angew. Chem. 95* (1983) 552; *Angew. Chem. Int. Ed. Engl. 22* (1983) 543.
[2] E. Ziegler, G. Kollenz, H. Igel, *Monatsh. Chem. 102* (1971) 1769.

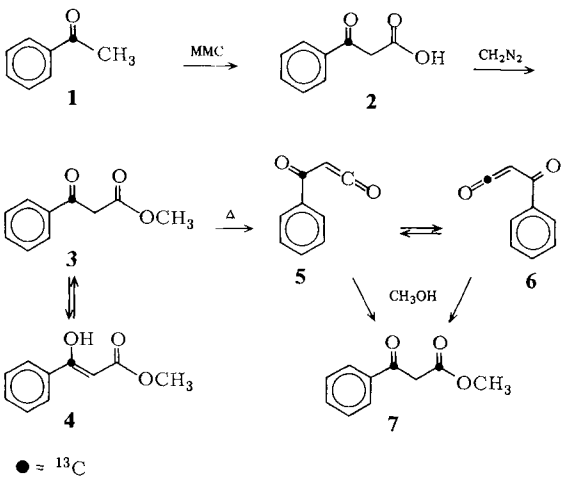
[3] **6**: m.p. = 183–184°C, crystallizes in the space group Pccn from toluene in the course of 3 months. Crystallographic data will be reported in a full paper in collaboration with Dr. *W. Massa*, Marburg.

[4] W. Stadlbauer, T. Kappe, *Z. Naturforsch. 36B* (1981) 739.

[5] **11**: $m/z = 266$; ^{1}H-NMR ($CDCl_3$, 400 MHz, −40°C): $\delta = 8.20$ (d, $J = 7.9$ Hz, 2H; H(C-7) and H(C-11)), 7.85 (d, $J = 8.2$ Hz, 2H; H(C-13) and H(C-17)), 7.2–7.8 (m, 6H); ^{13}C-NMR ($CDCl_3$, 100.6 MHz, −40°C): $\delta = 183.4$ (C-4), 182.3 (C-5), 166.4 (C-2), 136.8 (C-6), 136.4 (C-15), 133.5 (C-9), 133.4 (C-13, C-17), 129.7 (C-12), 129.3 (C-8, C-10), 128.9 (C-7, C-11), 128.3 (C-14, C-16), 125.0 (C-3) (for numbering, see formula **11**; the chemical shift assignments are based on ^1J and ^3J values).

[6] Collisional activation mass spectrometry of **13**, **14**, and the decomposition products, benzoyl(phenyl)acetylene and OCS, will be reported in a full paper in collaboration with Prof. *A. Maquestiau* and Dr. *R. Flammang*, State University of Mons, Belgium.

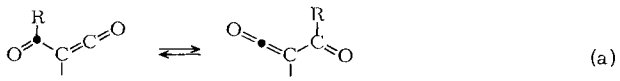
[7] C. Wentrup, K.-P. Netsch, *Angew. Chem. 96* (1984) 792; *Angew. Chem. Int. Ed. Engl. 23* (1984) 802.



A Novel Ketoketene–Ketoketene Rearrangement**

By *Curt Wentrup** and *Klaus-Peter Netsch*

In the previous communication[1] we reported experiments which led us to believe that acylketenes can undergo carbon scrambling via thermal 1,3-shift of a phenyl group [Eq. (a), R = Ph].



(a)

Since ketenes are important intermediates in numerous reactions, and many labeling studies have been carried out on the Wolff rearrangement[2], of which ketenes are the products, it is clearly of importance to determine whether the proposed ketoketene-ketoketene rearrangement [Eq. (a)] is realistic and general. We now wish to report a proof for this reaction using ^{13}C-labeled benzoylketene.

Treatment of [carbonyl-^{13}C]acetophenone **1**[3] (90 atom-%^{13}C) with methoxy(methoxycarbonyloxy)magnesium (MMC)[4] (dimethylformamide, 115°C, 1 h) gave [3-^{13}C]benzoylacetic acid **2** in 52% yield, which was converted into the methyl ester **3** (90%), the starting material for the study, by esterification with diazomethane (diethylether, 0°C). Compound **3** exists in solution as a mixture of the keto and enol forms **3** and **4**, respectively (^{1}H- and ^{13}C-NMR). Proof for the specific and complete (90 atom-%) incorporation of ^{13}C at C-3 in **3** is provided by observation of a ^{13}C-H coupling for the methylene group ($\delta = 4.0$) in the ^{1}H-NMR spectrum ($^2J_{^{13}C,H} = 6.2$ Hz). A central peak which originates from the CH_2 group of the unlabeled material had an integrated area ca. 10% of that of the total integral for the CH_2 group. Similarly, in the enol form **4** the signal for the vinylic H atom ($\delta = 5.66$) was split into a doublet ($^2J_{^{13}C,H} = 3.7$ Hz). In the ^{13}C-NMR spectrum the labeled carbonyl group in **3** appeared at $\delta = 192.2$, and a signal for the methylene group at $\delta = 45.5$ ($J_{^{13}C,^{13}C} = 40.5$ Hz). The enol C atom in **4** exhibited a signal at $\delta = 171.5$ ppm. In the IR spectrum of unlabeled **3**, two carbonyl bands appeared at 1685 (C=O) and 1740 cm^{-1} ($COOCH_3$). In ^{13}C-labeled **3** the former peak was shifted to 1650 cm^{-1}, whereas the latter remained unchanged[5].

Unlabeled benzoylketene **5** was generated by pyrolysis of unlabeled **3** (5 cm quartz tube, 700°C/10^{-4} torr). The pyrolysis product was isolated on a KBr disk at 82 K and the ketene identified by its intense, sharp absorption at 2133 cm^{-1} in the IR spectrum. This band disappeared on warming to 185 K due to reaction with the co-condensed methanol to re-form the starting material.

In the corresponding pyrolysis of labeled **3**, *two* ketene bands (intensity ratio ca. 55:45) appeared at 2133 and 2080 cm^{-1}, clearly showing that the ketene function now contained ca. 50% of the ^{13}C label[6]. Upon warming this ketene in the presence of methanol, the ester **7** was formed, in which *both* carbonyl groups were now labeled as seen, for example, by the appearance of *four* carbonyl bands in the IR spectrum (1650, 1685, 1710, and 1740 cm^{-1}) and *four* labeled C atoms in the ^{13}C-NMR spectrum (two from the keto, and two from the enol form of **7**)[7].

The thermal 1,3-shift of a phenyl group in a ketoketene has therefore been demonstrated (**5** ⇌ **6**). Furthermore, by pyrolyzing **3** at different temperatures, it was established that there is a significant activation energy for the phenyl group migration. At 400°C/10^{-4} torr *no* isotopic scrambling was observed: the ketene **5** ($\nu(CO) = 2133$ cm^{-1}) was the sole product. At 550°C ca. 50% rearrangement was observed, giving rise to two IR bands at 2133 and 2080 cm^{-1} in a ca. 2:1 ratio.

Although suprafacial thermal 1,3-shifts are "forbidden" by the rules of orbital symmetry[8], such shifts become possible in ketenes due to the presence of orthogonal orbitals. Further work is aimed at clarifying a dependence on the nature of the migrating group R in Eq. (a).

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[5] A Hooke's law calculation gives a value of 1649 cm^{-1} for the IR band of the ^{13}C keto CO group.

[6] A Hooke's law calculation gives a value of 2085 cm^{-1} for the IR band of the ^{13}C labeled ketene CO group.

[7] Keto form of **7**: $\delta = 192.2$ (C=O), 167.8 ($COOCH_3$). Enol form of **7**: $\delta = 171.5$ (C–OH), 173.5 ($COOCH_3$).

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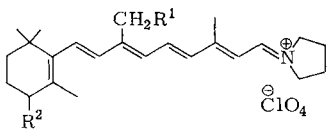
C=C Stretching Frequencies in Model Compounds of the Protonated Retinal Schiff Base**

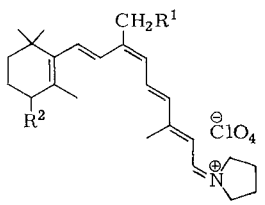
By *Timor Baasov* and *Mordechai Sheves**

Visual pigments and bacteriorhodopsin, the proton pump of the purple membrane of *Halobacterium halobium*, contain retinal chromophores (11-*cis* in the case of visual pigment and all-*trans* in bacteriorhodopsin) which is linked to a protein via a protonated Schiff base[1]. These pigments are transformed in a photochemical cycle into a number of intermediates possessing different absorption maxima. It is well established[2] that the absorption maxima of these species can be correlated with the C=C stretching frequencies observed in resonance Raman spectroscopy. Thus, a bathochromic shift of ca. 60 nm in λ_{max} is comparable to a shift of the C=C mode by ca. 20 cm^{-1} to lower frequency. It was first pointed out by *Rimai* et al.[3] that the position of the C=C stretching mode is a sensitive indication of charge delocalization. Thus, a decreased bond alternation results in a shift of the C=C bond stretching mode to higher frequency. According to a model proposed by *Nakanishi* and *Honig*[4], the shifts in λ_{max} of bovine rhodopsin and bacteriorhodopsin are regulated by through-space interaction of the chromophore with external negative charges.

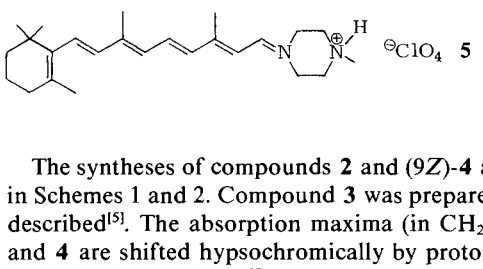
It is reasonable to assume that external charges influence the absorption of the photocycle intermediates. We therefore suggest that the changes observed in the C=C stretching frequency of visual pigments, bacteriorhodopsin, and the various photocycle intermediates may also originate from electrostatic interaction with non-conjugated charges introduced by the protein. To test this hypothesis, we have measured the C=C stretching frequencies of **2a**, **3a**, **4a**, and **5**, which bear positive charges at different positions of the retinal skeleton, by FT-IR spectroscopy.



1, $R^1 = R^2 = H$
2, $R^1 = (CH_3)_2N$, $R^2 = H$
2a, $R^1 = (CH_3)_2\overset{\oplus}{N}H$, $R^2 = H$
3, $R^1 = H$, $R^2 = (CH_3)_2N$
3a, $R^1 = H$, $R^2 = (CH_3)_2\overset{\oplus}{N}H$



4, $R^1 = R^2 = (CH_3)_2N$
4a, $R^1 = R^2 = (CH_3)_2\overset{\oplus}{N}H$



5

The syntheses of compounds **2** and (9*Z*)-**4** are described in Schemes 1 and 2. Compound **3** was prepared as recently described[5]. The absorption maxima (in CH_2Cl_2) of **2**, **3**, and **4** are shifted hypsochromically by protonation of the dimethylamino groups[5,6] in the vicinity of the polyene skeleton (**2a**, **3a**, and **4a**). However, a larger hypsochromic shift is observed in **4** ($\Delta\lambda_{max} \approx 50$ nm), which can be doubly protonated, than in **2** and **3** (Table 1).

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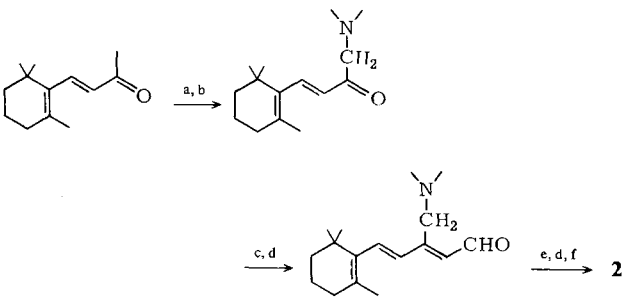
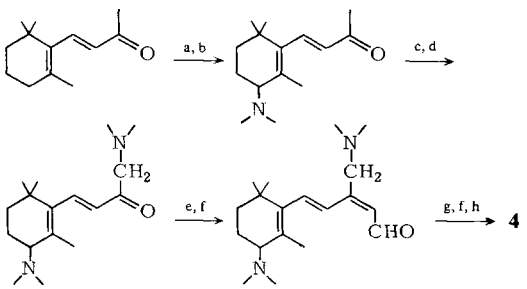
Table 1. UV/VIS absorption maxima and IR stretching frequencies of some model compounds of protonated and nonprotonated Schiff bases of retinal (measurements in CH_2Cl_2).

Compound	λ_{max} [nm]	$\Delta\nu$ [cm^{-1}] [a]	ν [cm^{-1}] C=C	ν [cm^{-1}] C=N$^{\oplus}$
1	492		1548	1626
2	487	2060	1550	1627
2a	442		1565	1629
3	469	850	1552	1626
3a	451		1561	1626
4	465	2650	1559	1627
4a	414		1574	1629
5	520		1534	1626

[a] Difference between the absorption maxima of the protonated and the nonprotonated species.



Scheme 1. a) 5,5-Dibromo-2,2-dimethyl-1,3-dioxane-4,6-dione/tetrahydrofuran (THF), RT, 12 h; b) $(CH_3)_2NH/K_2CO_3/THF$, RT, 1 h; c) $(EtO)_2P(O)CH_2CN/NaH/THF$, RT, 30 min; d) diisobutylaluminum hydride (dibal)/hexane, −78°C, 1 h/silicagel, −78°C to RT/separation of isomers; e) $(EtO)_2P(O)CH_2C(CH_3)=CHCN/NaH/THF$, RT, 1 h; f) pyrrolidine perchlorate/EtOH/0°C, 1 h.



Scheme 2. a) *N*-bromosuccinimide/CCl_4, reflux, 30 min; b) $(CH_3)_2NH/K_2CO_3/THF$, RT, 10 h; c) 5,5-dibromo-2,2-dimethyl-1,3-dioxane-4,6-dione/THF, RT, 12 h; d) $(CH_3)_2NH/K_2CO_3/THF$, RT, 1 h; e) $(EtO)_2P(O)CH_2CN/NaH/THF$, RT, 30 min; f) dibal/hexane, −78°C, 1 h/silicagel, −78°C to RT/separation of isomers; g) $(EtO)_2P(O)CH_2C(CH_3)=CHCN/NaH/THF$, RT, 1 h; h) pyrrolidine perchlorate/EtOH/0°C, 1 h.

Protonation of the dimethylamino groups in retinals **2**, **3**, and **4** also influences the position of the C=C stretching frequency (in CH_2Cl_2), shifting it to higher frequency. These C=C bands can be correlated with the UV/VIS-absorption maxima of the chromophores: a hypsochromic shift in the absorption spectrum is accompanied by a higher frequency of the C=C band (Fig. 1). Furthermore, comparison of the IR and UV/VIS spectra of **5** which possesses a positive charge in the vicinity of the alkylideneammonium ion, and of the pyrrolidine perchlorate of retinal reveals a bathochromic shift in the absorption spectra[7] and a shift to a lower frequency of the C=C stretching mode, in accordance with the results found for **2**−**4**.

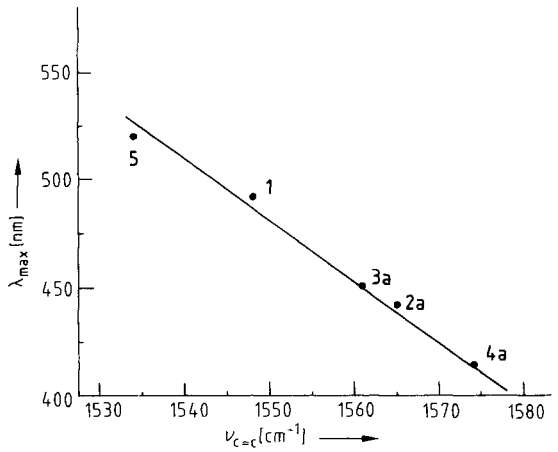


Fig. 1. Correlation between the C=C stretching frequencies and absorption maxima in the model compounds **1**, **2a**, **3a**, **4a**, and **5**.

It should be noted that protonation of the dimethylamino groups in the vicinity of the polyene skeleton in **2**—**5** does not significantly change the position of the C=N stretching frequency (Table 1). This result is consistent with the observed insensitivity of $\nu_{C=N}$ to λ_{max} in visual pigments[8].

Our results reveal that a positive charge in the vicinity of the retinal polyene decreases charge delocalization, causing an increase in the C=C frequency. However, an *external* positive charge near alkylideneammonium ion (**5**) increases the charge delocalization and decreases bond alternation, thus causing a shift of the C=C stretching mode to a lower frequency. It is evident that external positive charge affects not only the excited state but also the ground state.

The external point-charge model for bacteriorhodopsin assumes interaction with a negative charge in the vicinity of the ring moiety of the retinal skeleton. Here, we have investigated the effect of a positive charge, which is expected to give an opposite effect. However, the observation that a *positive* charge influences the absorption maximum and the C=C stretching frequency of a protonated retinal Schiff base supports the external point-charge model for bacteriorhodopsin and also our assumption that the different C=C stretching frequencies found in bacteriorhodopsin, visual pigments, and their photochemically induced intermediates may originate from through-space interaction with external negative charges.

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Vanadium Thiolate Complexes with VS_5- and VOS_4-Centers: Synthesis and Structure of $[VS(SC_2H_4S)_2]^{2\ominus}$ and $Na_2[VO(SC_2H_4S)_2]\cdot 8\,MeOH$**

By *Detlef Szeymies, Bernt Krebs,* and *Gerald Henkel**

The importance of S(Cys)-metal bonds in a variety of metalloproteins has created a general interest in the thiolate chemistry of biologically essential trace elements, one of which is vanadium. Investigations on the problem of V-nitrogenase[1,2] have furnished evidence of a possible vanadium-sulfur coordination in proteins. The anion $[VS(edt)_2]^{2\ominus}$ **1** ($edt^{2\ominus}$ = ethane-1,2-dithiolate) and the salt $Na_2[VO(edt)_2]\cdot 8\,MeOH$ **2** mentioned in the title, as well as the anion $[VO(edt)_2]^{2\ominus}$ **3** occurring in solutions of **2** and the polynuclear complexes $[V_2(edt)_4]^{2\ominus}$ **4** and $[Fe_2VS_4(SPh)_4]^{3\ominus}$[3], could be useful as reference compounds for the identification of vanadium-sulfur centers in metalloproteins.

On reaction of $VS_4^{3\ominus}$ with $[V_2(edt)_4]^{2\ominus}$ or with an excess of $edt^{2\ominus}$ in methanol, **3** is formed as main product together with the thiovanadyl complex $[VS(edt)_2]^{2\ominus}$ **1**, which crystallizes as $(Ph_4P)_2[VS(edt)_2]\cdot MeOH$ **5** in the form of brownish-red columns along with green $Na_2[VO(edt)_2]\cdot 8\,MeOH$ **2** after addition of Ph_4PBr[4]. **3** is also formed on oxidation of **4** with Na_2S_2 in methanol, or from $[VO(acac)_2]$ ($acac^{\ominus}$ = acetylacetonate) by ligand exchange reaction[3c]. Besides [VS(acen)] **6** ($acen^{2\ominus}$ = *N,N'*-ethylenebis(acetylacetonylideneamine) dianion)[5], the mononuclear anion **1** is the second thiovanadyl complex whose structure could be determined; furthermore, **1** is the first pentacoordinated vanadium complex with a complete sulfur ligand sphere and also the first sulfide-thiolate complex of vanadium.

The anions **1** (Fig. 1) contain metal centers which are surrounded by four S atoms of two $edt^{2\ominus}$ ligands and one

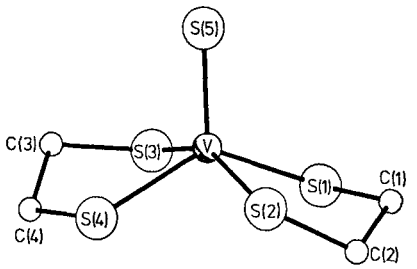

Fig. 1. Structure of the anion **1** in crystals of **5** with assignment of atoms (H atoms omitted). Important bond lengths [Å]: V-S_a 2.098(2), V-S_b 2.348(2)—2.386(2); range of angles [°]: S_a-V-S_b 103.48(7)—113.88(7); S_b-V-S_b 82.96(6)—85.86(6) and 132.54(6)—152.96(6) (S_a = S(5); S_b = S(1)—S(4)).

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inorganic S atom. The coordination polyhedron is a strongly distorted square pyramid with the sulfide substituent located at the axial position. The V=S bond in **1** (2.098(2) Å) is slightly longer than in **6** (2.061(1) Å). The other V–S bonds (2.348(2)–2.386(2) Å) are on average about 0.02 Å shorter than those of the oxovanadyl compound **2**.

In contrast to **1**, **3** can be isolated from methanol as the solvated sodium salt **2** (Fig. 2). In crystals of **2**, which are extremely sensitive because of the high methanol content, the metal atom is surrounded by four almost coplanar thiolate S atoms at a distance of 2.387 Å (mean value) as well as an O atom at a distance of 1.607(6) Å. This O atom is additionally bonded to two Na atoms which occupy the centers of two oxygen octahedra which share a common face. The eight methanol O atoms participate in the Na coordination (Na···(μ_2-O) 2.430(5)–2.490(5) Å, Na···O_{term} 2.288(6)–2.407(6) Å). The Na atoms are separated by 3.283(3) Å from each other and by 3.775(3) Å from vanadium. As the Na atoms occupy coordination sites in crystals of **2** which are characteristic for transition metal atoms, **2** can also be described as a neutral vanadium-sodium complex that is stabilized by solid-state effects.

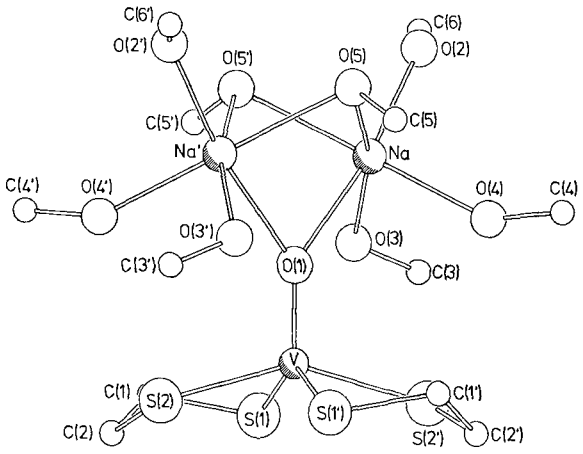

Fig. 2. Structure of **2** in crystals with assignment of atoms (H atoms omitted). Important bond lengths [Å]: V-O(1) 1.607(6), V-S(1) 2.366(2), V-S(2) 2.407(2); range of angles [°]: O(1)-V-S 104.8(1)–109.9(1); S-V-S 84.71(7)–85.35(7) and 140.26(8)–150.45(8).

In the context of the formation of **1** and **3** from $VS_4^{3\ominus}$, the mechanistic aspects are of interest. In the course of the reduction of $VS_4^{3\ominus}$, **1** is presumably the immediate precursor of **3**, which is formed in a subsequent step by substitution of the thiovanadyl S atom. For the formation of **1** there are several conceivable mechanisms in which mixed complexes such as $[VS_x(edt)_y]^{n\ominus}$ $(9 > x+2y > 3)$ could occur as intermediates. Thus, e.g., the (hypothetical) complex $[VS_2(edt)_2]^{3\ominus}$ with a sixfold sulfur coordination would be a thio-analogue of the well known dioxovanadium(V) compounds such as $(NH_4)_3[VO_2(C_2O_4)_2]$[6]. The fact that a rhenium analogue of **1**, namely $[ReS(edt)_2]^{\ominus}$, is known[7], confirms once again the principle of cross-relationship; the existence of mononuclear sulfide-ethanedithiolate complexes of molybdenum can also be expected.

The V=O stretching frequencies determined by IR spectroscopy in crystals of **2** (948 cm^{-1}) and in $(Me_4N)Na[VO(edt)_2]\cdot 2\,EtOH$[3c] (928 cm^{-1}) are correlated with the V=O bond lengths (1.607(6) and 1.625(2) Å, respectively). The V=S stretching vibration of **5** (ca. 515 cm^{-1}) is comparable with those of [VS(salen)] (salen$^{2\ominus}$ = *N,N'*-ethylene(salicylideneamine) dianion) and **6** (543 and 556 cm^{-1}, respectively)[8].

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2, 92315-39-4; **4**, 87495-20-3; **5**, 92315-37-2; VS_4^{3-}, 14791-51-6; methanol, 67-56-1

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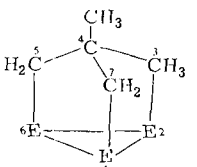
Synthesis of an all-*cis*-Organocyclotriphosphane (P_3-Nortricyclane) and its Pentacarbonylchromium Complex**

By *Jochen Ellermann** and *Alfons A. M. Demuth*

Dedicated to Professor Ekkehard Lindner on the occasion of his 50th birthday

We have previously reported the nortricyclanes **1a**[1], **b**[2], which contain an Sb_3- and an As_3-ring, respectively. The complex chemistry of the homologous phosphorus compound **1c** is of particular interest, since, of the structurally analogous heteronortricyclanes $P(SiMe_2)_3P_3$[3] and $(Me_3Si)_3P_7$[4], only the latter surprisingly exhibits no coordination tendencies[5].



1a, E = Sb
1b, E = As
1c, E = P

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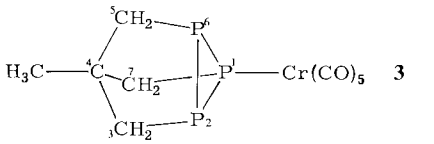
Whereas **1a**, **b** are accessible from $CH_3C(CH_2EPh_2)_3$ (E = Sb, As) via selective cleavage of the phenyl groups with HCl and HI, respectively, followed by reduction of the initially formed products $CH_3C(CH_2SbCl_2)_3$ or $CH_3C(CH_2AsI_2)_3$ with sodium, this method cannot be used for the preparation of **1c** since $CH_3C(CH_2PPh_2)_3$ does not undergo selective phenyl-group cleavage with hydrogen halides[6]. 4-Methyl-1,2,6-triphosphatricyclo[2.2.1.$0^{2,6}$]heptane **1c** was therefore synthesized in a batch reaction from 1,3-dibromo-2-bromomethyl-2-methylpropane **2** and NaP/KP[7] in refluxing monoglyme.

$$\underset{\mathbf{2}}{CH_3C(CH_2Br)_3} + 3\,MP \xrightarrow{80\,^\circ C} \mathbf{1c} + 3\,MBr \qquad M = Na,\ K$$

The composition and structure of the colorless, crystalline **1c** are based on the results of elemental analyses and spectroscopic studies (^1H- and ^{31}P-NMR, Raman, MS (FD, EI)[8]). **1c**, which is readily oxidized in solution, can be sublimed and is highly soluble in tetrahydrofuran (THF) and di- and trichloromethane, moderately soluble in benzene, diethyl ether, and heptane, sparingly soluble in methanol, and insoluble in acetone and water. The $^1H\{^{31}P\}$-NMR spectrum ($CDCl_3$, TMS int.) of **1c** exhibits two singlets at $\delta = 1.30$ (6H, CH_2) and 1.50 (3H, CH_3); in the $^{31}P\{^1H\}$-NMR spectrum (rel. 85% H_3PO_4) only one singlet at $\delta = -203.7$ occurs. The most intense band in the Raman spectrum of a solution of **1c** in CH_2Cl_2 (530 (p) cm^{-1}) is assigned to the A_1 stretching frequency of the P_3-ring; assuming C_{3v} molecular symmetry, we assign the medium-strong band at 394 (dp) cm^{-1} [IR (KBr): 394 (m) cm^{-1}] to the $\nu(P_3)$ vibration (E).

$Cr(CO)_5 \cdot thf$, prepared by UV irradiation of hexacarbonylchromium(0) in THF, reacts with **1c** in the molar ratio 1:1 to give the complex **3** (molecular symmetry: C_s, local symmetry of the $PCr(CO)_5$ group: C_{4v})[9].



3

η^1-Coordination of **1c** to $Cr(CO)_5$ splits the $\nu(P_3)$ band (E) at 394 cm^{-1} in the Raman spectrum [391 (vs, p) and 403 (m, dp) cm^{-1}, A′ + A″]; simultaneously, a new band of medium intensity occurs at 179 (p) cm^{-1}, which we assign to the Cr–P stretching frequency. Because only one P atom is coordinated in **3**, the $^{31}P\{^1H\}$-NMR spectrum[9] exhibits the eight lines of an AB_2 system, corresponding to the A_2B systems of cyclotriphosphanes with C_s symmetry[10].

Procedure

All operations were performed in a nitrogen atmosphere in anhydrous solvents. — **1c**: Na/K alloy (18.9 mL, 542 mmol) is added dropwise directly to a vigorously stirred suspension of white phosphorus (15.2 g, 492 mmol) in 300 mL monoglyme at 80°C. After 3 h at 80°C, **2** (24.8 mL, 164 mmol) is added dropwise and the mixture refluxed for 4 h. After filtration and removal of the solvent, **1c** is separated by sublimation and recrystallized from THF. Yield 2.5 g (9.4%), colorless crystals, m.p. = 128°C. — **3**: A stirred solution of $Cr(CO)_6$ (455 mg, 2.07 mmol) in 50 mL THF is irradiated for 3 h with UV light, and the solution added dropwise over 5 min to a solution of **1c** (290 mg, 1.79 mmol) in 20 mL THF. After stirring for 1 h at 20°C, the solvent is removed and unreacted $Cr(CO)_6$ sublimed out at 70°C, 1 Pa. The residual solid is taken up in 5 mL CH_2Cl_2 and insoluble material filtered off. The yellow solution is evaporated almost to dryness, and precipitated **3** dissolved in 2 mL pentane and 0.4 mL CH_2Cl_2 (heating). After cooling to −20°C, analytically pure **3** crystallizes: yield 201 mg (32%), yellow crystals, m.p. = 100°C.

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CAS Registry numbers:
1c, 92366-00-2; **2**, 60111-68-4; **3**, 92366-01-3; $Cr(CO)_5 \cdot thf$, 15038-41-2

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[8] MS: *m/z* 162 ($M^{\oplus}$, 100%), 147 ($M^{\oplus} - CH_3$, 5), 117 ($M^{\oplus} - CH_2P$, 6), 116 ($M^{\oplus} - CH_3P$, 5), 107 (CH_2P_3, 5), 100 ($M^{\oplus} - P_2$, 20), 93 (P_3, 6), 85 ($C(CH_2)_3P$, 11), 75 (CHP_2, 6), 69 ($CH_3C(CH_2)_3$, 6), 55 ($CH_3C(CH_2)_2$, 11), 45 (CH_2P, 6).
[9] MS: *m/z* 354 ($M^{\oplus}$, 17%), 214 ($M^{\oplus} - 5CO$, successively, 94), 162 (**1c**, 6), 145 (CrP_3, 2), 114 (CrP_2, 8), 80 (CrCO, 6), 52 (Cr, 100). Data are relative to ^{52}Cr. The isotopic patterns correspond to expectations. IR (KBr): 2065, 1988, 1960, 1927, 1905; (CH_2Cl_2): 2065, 1992, 1947 cm^{-1} (CO). Raman (solid): 2063, 1987, 1976, 1941, 1930 (CO); 557, 411, 398 (P_3); 184 (CrP); (CH_2Cl_2): 2066 p(A_1), 1989 dp(B_1), 1935 dp(E) (CO); 555 p(A′), 403 dp(A″), 391 p(A′) (P_3); 179 p(A′) (CrP) cm^{-1}. $^1H\{^{13}P\}$-NMR ($CDCl_3$, TMS int.): $\delta = 1.50$ (s, CH_3), $\delta(A) = 1.60$, $\delta(B) = 1.46$ (AB system, $J(AB) = 13.8$ Hz, 3,5-CH_2), 1.70 (s, 7-CH_2); $^{31}P\{^1H\}$-NMR ($CDCl_3$, H_3PO_4 ext.): $\delta(A) = -93.0$, $\delta(B) = -209.2$ (AB_2 system, $J(AB) = 220$ Hz), A ≙ P1, B ≙ P2,6.
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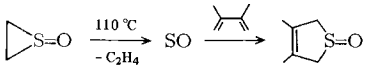
Stabilization of Sulfur Monoxide by Coordination to Transition Metals**

By *Wolfdieter A. Schenk**, *Johanna Leissner*, and *Christian Burschka*

Sulfur monoxide, SO, is one of the classical, unstable small molecules[1,2]; herein we report on its stabilization by incorporation into square-planar rhodium and iridium complexes. Compounds with an SO bridge between two[3] and three[4] metal centers are already known, but, consistent with their mode of formation, they are better regarded as oxidized sulfido clusters; the constitution of two complexes reportedly having terminal SO ligands[5,6] is still controversial. Complex-stabilized S_2O and S_2O_2 are obtained by oxidation of $[(dppe)_2IrS_2]^{\oplus}$ (dppe = $Ph_2PCH_2CH_2PPh_2$)[6,7].



Sulfur monoxide can be generated in solution by thermolysis of thiirane *S*-oxide **1**[8] and trapped with, e.g., 1,3-dienes[9]. We have prepared SO-complexes by fragmentation of **1** in the coordination sphere of a transition metal;

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the SO is thus stabilized immediately on formation[5]. When the 14-electron complexes **2** and **3**[10] (which are readily obtainable in solution) are allowed to react with **1** at −70 °C and 0 °C, respectively, the deep-green crystalline products **4** and **5** (correct elemental analyses) are formed in moderate to good yields[11]. On carrying out ^{31}P-NMR spectroscopic investigations at low temperature, we were able to detect momentarily stable intermediates, presumably adducts of **1** and the coordinatively unsaturated complexes **2** and **3**.

$$[M(PiPr_3)_2Cl] \xrightarrow{+\,1} [M(PiPr_3)_2(C_2H_4SO)Cl] \xrightarrow{-C_2H_4} [M(PiPr_3)_2(SO)Cl]$$

2, M = Rh; **3**, M = Ir

4, M = Rh; **5**, M = Ir

Table 1. Spectroscopic data of the SO complexes **4** and **5**.

Complex	IR (Nujol) [cm^{-1}]	^{31}P-NMR ([D$_8$]toluene) δ	^1J(Rh–P) [Hz]	MS m/z ($M^{\oplus}$)
4	1075 s ν(SO), 455 m δ(RhSO), 341 m ν(RhCl), 271 m ν(RhS)	42.4	153	506
5	1071 s ν(SO), 475 m δ(IrSO), 337 m ν(IrCl), 279 m ν(IrS)	28.1		596

According to spectroscopic investigations (Table 1), the new compounds have a square-planar structure with the bulky phosphane ligands arranged *trans* to each other and the M–S=O moiety in an angular disposition. Such an array is confirmed by the X-ray structure analysis of the iridium complex **5** (Fig. 1). The metal atom is located in an almost square but perfectly planar environment [Ir–P 237.1(2), Ir–Cl and Ir–S 223.6(3) pm (disorder between Cl and S in the space group $P2_1/c$)]. The SO-group [S–O 132(2) pm, Ir–S–O 130(1)°] is turned through an angle of 20° from the plane of coordination. **4** and **5** are thus closely related to the corresponding SO_2-complexes[12].

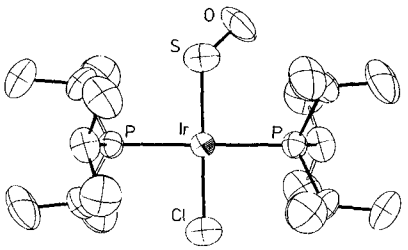

Fig. 1. Structure of the complex **5** in the crystal. Space group $P2_1/c$ (No. 14), $Z=2$, $a=8.128(3)$, $b=9.075(3)$, $c=16.659(4)$ Å, $\beta=93.18(3)°$, $\rho_{calc}=1.62$, $\rho_{exp}=1.615$ mg/mm^3, $R_1=0.028$ (0.034), $R_2=0.036$ (0.037) for 1772 (2167) reflections ($I_{obs}>3\sigma(I)$). Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2 on quoting the CSD number 51005, the names of the authors, and the journal citation.

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A Facile Route to 1,4,7-Trithiacyclononane

By *Dieter Sellmann** and *Lothar Zapf*

Although the synthesis of crown ethers and related compounds has attained a high standard[1], medium-sized heterocyclic rings of this type are still difficult to obtain. For example, 1,4,7-trioxacyclononane and 1,4,7-trithiacyclononane (TTCN) were previously only accessible in 1–4% yield[2,3]. The conformation adopted by TTCN is the theoretically most stable in which the three S atoms are *endo*-orientated[4]. This "frozen" conformation is probably the reason why TTCN forms surprisingly stable Ni^{II}, Co^{II}, and Cu^{II} complexes, which have recently been the center of interest as model compounds for metal-sulfur enzyme centers and electron-transfer reactions[3b,5]. In the meantime, the yields of TTCN obtained via high-dilution reactions could be increased from 0.04 to 4.4%[3], but these are still too low to permit more thorough studies of the chemistry of TTCN.

In the course of investigations of the reactivity of sulfur-coordinated metal centers, we have now discovered a route involving a "template" alkylation reaction which affords TTCN straightforwardly and in 60% yield. Since the starting complex is regenerated in the third reaction step, the synthesis can, in principle, be performed catalytically.

Treatment of $[Mo(CO)_3(CH_3CN)_3]$ **1**[6] with an equimolar amount of bis(tetramethylammonium) 3-thia-1,5-pentanedithiolate **2** furnishes yellow crystals of the previously unknown complex **3** in 95% yield [ν_{CO}(DMSO) 1865, 1740, 1710 cm^{-1}; ^{1}H-NMR ([D$_6$]DMSO): $\delta=3.2$ (24, s), 2.0–2.9 (8, m)]. Subsequent equimolar reaction with 1,2-dibromoethane affords the neutral complex **4** smoothly in 98% yield [ν_{CO}(DMSO): 1925, (A_1), 1815 cm^{-1} (E); ^{1}H-NMR ([D$_6$]DMSO): $\delta=2.65$ (s)]. The title compound TTCN can be liberated in the third step of the reaction by treating **4** with **2**, and at the same time **3** is regenerated in 84% yield. **3** can be realkylated to **4**[7].

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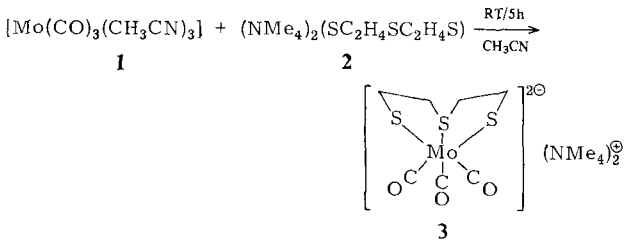

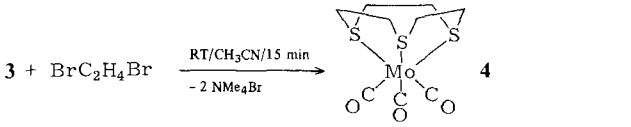

Procedure:

3: **1** (6.06 g, 20 mmol) and **2** (6 g, 20 mmol) in 120 mL CH_3CN are stirred for 5 h at room temperature, in the course of which yellow **3** precipitates. The mixture is cooled to -20 °C, the precipitate filtered off, washed with tetrahydrofuran and dried to yield 9.12 g analytically pure **3** (95%).—**4**: **3** (8.64 g, 18 mmol) is suspended in 150 mL CH_3CN and stirred with $BrCH_2CH_2Br$ (3.4 g, 18.1 mmol) for 15 min at room temperature. The precipitate of pale yellow **4** is filtered off, washed with MeOH (5 × 40 mL) to remove NMe_4Br, and dried. Yield: 6.35 g (98%).—TTCN: A mixture of **4** (6 g, 16.7 mmol) and **2** (5 g, 16.7 mmol) in 50 mL dimethyl sulfoxide (DMSO) is stirred for 48 h at room temperature and subsequently extracted with Et_2O (3 × 100 mL). EtO_2 is removed in vacuo from the combined extracts at room temperature. TTCN dissolved in the remaining DMSO is precipitated with 200 mL H_2O, filtered off, and recrystallized from MeOH. Yield 1.8 g (60%) analytically pure TTCN (^{1}H-NMR (CCl_4): $\delta = 3.15$; MS (EI): *m/z* 180 ($M^{\oplus}$).—In the extraction, regenerated **3** remains as a highly viscous, yellow paste; stirring for 1 h with 80 mL CH_3CN gives 6.73 g crystalline **3** (84%).

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1, 15038-48-9; **2**, 92314-36-8; **3**, 92314-33-5; **4**, 92314-34-6; TTCN, 6573-11-1; $Br(CH_2)_2Br$, 106-93-4

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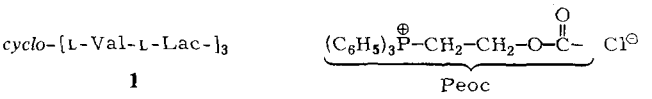
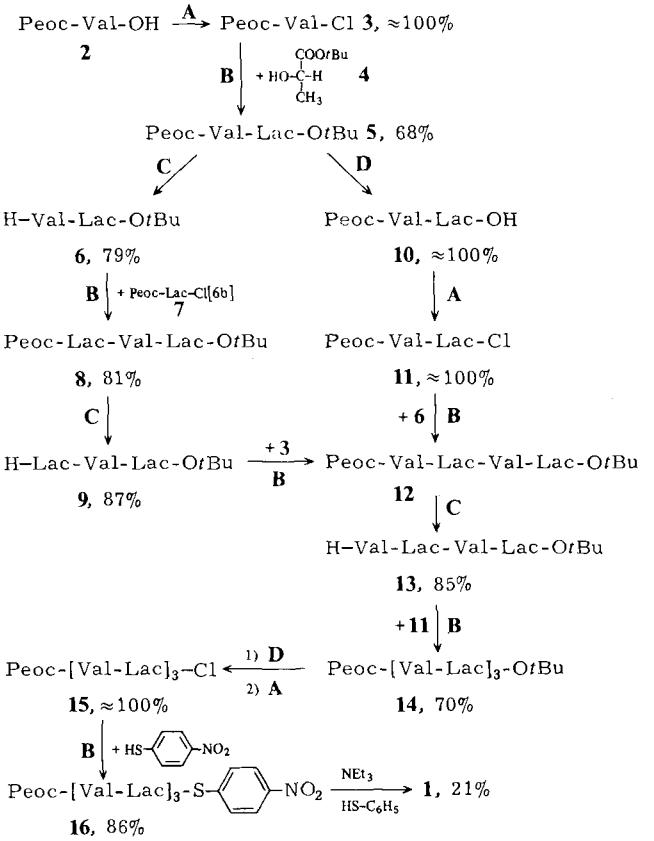
Synthesis of the all-L-Configurated Cyclohexadepsipeptide *cyclo*-[L-Val-L-Lac]$_3$ by the Peoc/Acid Chloride Method**

By *Horst Kunz** and *Hans-Georg Lerchen*

Because of their antibiotic and complexing effects[1], depsipeptides are interesting objects for synthesis. Compared to peptides, the synthesis of depsipeptides is complicated by the presence of the ester groups. If α-hydroxy carboxylic acids are members of the chain, active esters are involved. The synthesis of depsipeptides therefore requires considerable carboxy activation. These difficulties impair particularly the cyclization step in both the acid chloride[2], the phosphite[3], or active ester method[4]. In addition, the cyclization yields are particularly low if all the building blocks have the same configuration and the amino acids contain no *N*-methyl groups[5]. In the cyclohexadepsipeptide **1**, which consists of alternating L-valine and L-lactic acid moieties, all these complicating factors are combined.



For the synthesis of **1**, we investigated the efficiency of the acid chloride method using building blocks consisting of 2-(triphenylphosphonio)ethoxycarbonyl(Peoc)-protected amino acids and hydroxy acids[6]. Linear depsipeptides are synthesized both by single-step chain extension and by coupling two building blocks (Scheme 1).



Scheme 1. **A**: $(COCl_2)$ in CH_2Cl_2; **B**: pyridine/CH_2Cl_2/0 °C; **C**: $HN(CH_3)_2/CH_3OH$/0 °C; **D**: HCl/CH_2Cl_2/room temperature.—Val and Lac have L-configuration. The step **13**→**14** can be carried out analogously to **6**→**12**. Yield: **11**→**12**: 66%.

The basic building block **5** for both synthetic routes is obtained from Peoc-valine chloride **3**[6b] and *t*-butyl L-lactate **4** and deblocked at the *N*-terminal to afford the amino component **6**.

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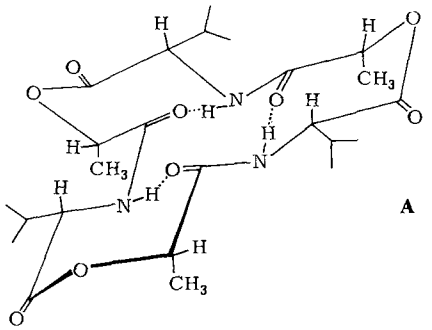
A process of alternately coupling the Peoc-protected single building blocks (and the double building block **11**) and mild basic deblocking (Scheme 1, left half) leads to the protected hexadepsipeptide **14**. In previous syntheses, the late formation of the esters of the oligodepsipeptides was not possible.

Alternatively, the chain can be constructed by linking ester-like bound didepsipeptides, whereby the reactivity of the Peoc-protected acid chloride **11** is exploited (Scheme 1, right half). By this means, **14** is attained in a few steps. The physical data[7] of crystalline samples of **14** prepared by the two routes are mutually consistent.

The advantages presented by the Peoc/acid chloride method became clear in the cyclization of **14** to **1**, a step which appeared to be almost unrealizable in view of the experiences reported by *Shemyakin* et al.[5]. **14** is deblocked at the *C*-terminal and converted into the acid chloride **15**. In order to avoid that the carboxy activation is lost upon removal of the Peoc group by base, the *p*-nitrophenyl thioester **16** is prepared, from which the Peoc group can be removed by trimethylamine/thiophenol[8] in dilute acetonitrile solution. Despite numerous side reactions, the fact that 1) all the building blocks have the same configuration and 2) *N*-methyl groups are absent, the intramolecular aminolysis nevertheless affords the cyclohexadepsipeptide **1** in 21% yield after chromatography. The structure of **1** is confirmed by the FD and FAB mass spectra (base peak *m/z* 514 $(M+1)$[9]). Of particular note is that the 400-MHz ^{1}H-NMR spectrum exhibits only one signal, respectively, for the amide protons, the methine protons of the lactic acid residue, those of the valine moiety, and for the side-chain protons. From this it has to be concluded that conformation **A** with C_3 symmetry is preferred in chloroform.



A

It is clear from **A** why the cyclization of depsipeptides consisting of building blocks having the same configuration is so strongly hindered: The side chain of every second building block (in **A** the lactic acid) is constrained to occupy the "axial" position.

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1, 92269-64-2; **2**, 84622-64-0; **3**, 82414-77-5; **4**, 13650-10-9; **5**, 92269-65-3; **6**, 13498-72-1; **7**, 84569-71-1; **8**, 92284-03-2; **9**, 92269-66-4; **10**, 92269-67-5; **7**, 92269-68-6; **12**, 92284-04-3; **13**, 92344-03-1; **14**, 92269-69-7; **15**, 92269-70-0; **16**, 92269-71-1; *p*-nitrophenylthiol, 1849-36-1

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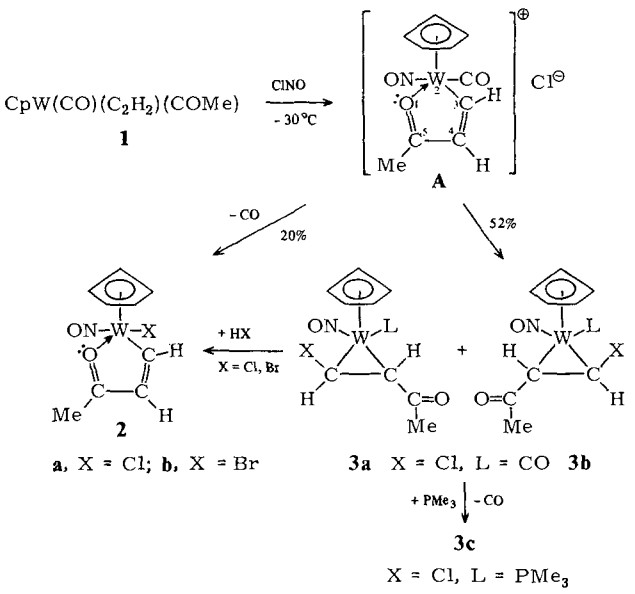
[7] Correct elemental analysis; $[\alpha]_D^{22} = -65.3$ ($c = 1.2$, CH_3OH).
[8] Thiophenol serves as a trapping nucleophile for the vinylphosphonium salt; see H. Kunz, *Chem. Ber. 109* (1976) 2670.
[9] Interestingly, in the FAB-MS recorded in tetraethylene glycol a peak occurs at *m/z* 619 which corresponds to an adduct of diethylene glycol and **1**.
[10] The low-field position of the N–H doublet ($\delta = 7.15$) in **1** and the result that the quartet of the lactic acid methine proton ($\delta = 5.23$) is shifted to low field relative to the corresponding signal of comparable open-chain compounds (e.g. **13**) by ca. 0.15, while the doublet of doublet of the valine methine proton ($\delta = 4.33$), in contrast, is shifted to high field by ca. 0.25, suggests the following: In the preferred conformation, the isopropyl side chains adopt approximately equatorial positions, whereas the methyl groups in the lactic building blocks must be practically axially orientated. The position of the ester carbonyl bands ($\nu = 1755\ cm^{-1}$) and those of the associated typical amide I bands of the amide groups at $\nu = 1650\ cm^{-1}$ are also consistent with conformation **A**.

Unusual Conversion of an Alkynetungsten Complex into a Tungstenacyclopropane Compound by Nitrosyl Chloride**

By *Helmut Guido Alt**, *Heidi Ingrid Hayen*, *Heinz-Peter Klein*, and *Ulf Thewalt*

Neutral transition-metal carbonyl complexes typically react with nitrosyl chloride to give chloronitrosyl complexes[1]. The reaction of the acetylalkyne complex **1**[2] with ClNO also affords, via insertion of the alkyne ligand into the tungsten-acetyl bond, a chloronitrosyl complex **2**, but as a minor product. The major products isolated are



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the tungstenacyclopropane complexes **3a**, **b**, which are characterized by IR, ^{1}H-NMR, ^{13}C-NMR, and mass spectroscopy. Only two of the four possible diastereomers, those with *trans*-oriented hydrogen atoms on the three-membered ring, are observed.

From **3a**, **b**, novel tungstenacyclopropane complexes are accessible which cannot be prepared by photoinduced substitution reactions of the parent compound $CpW(CO)_2NO$ with olefins. We infer that the cationic intermediate **A** can be attacked by its $Cl^{\ominus}$ counterion both at the tungsten atom to form **2a** and at C-3 to afford **3a**, **b**.

The description of the bonding in **3a**, **b** as tungstenacyclopropanes and not olefin complexes derives from the ^{1}H- and ^{13}C-NMR spectra (Tables 1 and 2), which indicate that the atomic nuclei of the three-membered ring are strongly deshielded. Also the magnitude of ^3J(H,H) (**3a**, 9.0; **3b**, 8.4 Hz) is characteristic of a metallacyclopropane. Furthermore, ^2J(W,H) as well as ^1J(C,H) and ^1J(W,C) are observed (Tables 1 and 2), couplings that are typical for cyclopropane[4] and for the metallacyclopropane complexes $Cp_2MoC_2H_4$[5], $Cp_2Ta(C_2H_4)H$[6], and $Cp(CO)_2\overline{MCH(PMe_3)-CHCOR}$ (M = Mo, W; R = alkyl)[7]. The ^{1}H-NMR spectra of **3a**, **b** at different temperatures in [D$_8$]toluene reveal that there is no rotation which would be expected for a π-"olefin" type bonding. The reaction of **3a**, **b** with the strong donor trimethylphosphane, which substitutes not an "olefin" but rather the CO ligand, is also evidence against the formulation as an olefin complex. Thus, the diastereomerically pure tungstenacyclopropane **3c** (Tables 1 and 2) is formed. In contrast, the olefin ligand in $Fe(CO)_4(ClHC{=}CHCOMe)$ is easily displaced, even by the weak donor NMe_3[3]. **3a** and **3b** are transformed by gaseous HCl and HBr (or Br_2) into **2a** and **2b**, respectively, without elimination of an alkene or alkane.

The X-ray structure analysis of **3a** corroborates the interpretation of the spectroscopic results. Tungsten displays approximately square-pyramidal coordination, and the atomic distances are those expected for a metallacyclopropane complex[7].

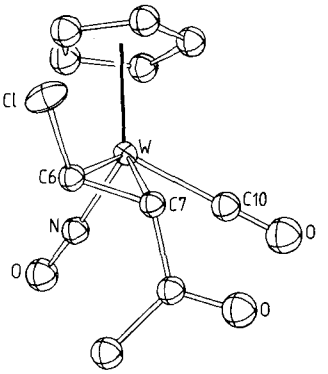

Fig. 1. Crystal structure of **3a**. Selected bond lengths [Å] and angles [°]: W–C6 2.213, W–C7 2.272, C6–C7 1.451, W–C10 1.983, W–N 1.802; C6–W–C7 37.7(4), W–C6–C7 73.3(6), W–C7–C6 68.9(6). Further details of the crystal structure investigation can be obtained from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, by quoting the depository number CSD 50998, the names of the authors, and the journal citation.

Table 1. IR- [a] and ^{1}H-NMR data [b] of **2** and **3**.

	ν(CO)	ν(NO)	δ(Cp)	δ(C$_2$H$_2$) [^3J(H,H)]	δ(Me)	δ(PMe$_3$)
2a	1545	1635	5.89	10.47 (d)/7.64 (d) [c]	2.54	—
2b	1543	1638	5.91	10.54 (d)/7.51 (d) [8.3]	2.55	—
3a	2005 [d] 1658	1640 [e] [f]	5.81	5.07 (d)/3.08 (d) [g] [9.0]	1.93	—
3b	1985 [d] 1678	1610 [e]	5.60	4.87 (d)/3.52 (d) [h] [8.4]	2.39	—
3c	1642	1580	5.70 [i]	4.48 (d, d) [k]/3.16 (d) [l] [6.3]	1.89	1.75 (d) [m]

[a] [cm^{-1}] (THF). [b] CD_2Cl_2, −20 °C; J [Hz]. [c] ^2J(W,H) = 8.8. [d] In KBr. [e] ν(C–Cl) = 760. [f] Not clear. [g] ^2J(W,H) = 4.6. [h] ^2J(W,H) = 5.4. [i] d, J(P,H) = 1.7. [k] ^3J(P,H) = 11. [l] ^2J(W,H) = 4.9. [m] ^2J(P,H) = 10.0.

Table 2. ^{13}C-NMR data [a] of **2** and **3**.

	δ(Cp) [^1J(C,H)]	δ(CO)	δ(C$_2$H$_2$) [^1J(C,H)]	δ(Me) [^1J(C,H)]	δ(PMe$_3$) [^1J(C,H)]
2a	102.8 [182.1]	212.0	237.4/135.2 [151.3/166.2]	26.4 [129.1]	—
2b	102.4 [182.6]	212.6	225.5/135.1 [150.4/168.0]	26.4 [128.5]	—
3a	99.0 [181.6]	208.3 204.0	55.0/42.2 [b] [182.6/152.2]	26.2 [126.0]	—
3b	97.4 [180.6]	209.9 207.3	59.6/51.4 [c] [182.6/177.2]	31.0 [125.0]	—
3c	97.6 [177.8]	203.6	57.2 [d]/40.8 [178.6/153.9]	26.8 [126.5]	16.9 [e] [129.9]

[a] CD_2Cl_2, −20 °C; J [Hz]. [b] ^1J(W,C) = 48.8/31.7. [c] ^1J(W,C) = 14.6/11.0. [d] ^2J(P,C) = 17.9. [e] ^1J(P,C) = 35.0.

Procedure:

2a, **3a**, **b**: **1**[2] (0.18 g, 0.52 mmol) is dissolved in 50 mL CH_2Cl_2 and 0.8 mL ClNO in CH_2Cl_2 (0.7 mol/L) added to the stirred solution at −30 °C. In the subsequent column chromatographic separation (silica gel/pentane), yellow **3a**, **b** (toluene/ether 5 : 1) and orange **2a** are eluted (ether). After removal of the solvent, the products are crystallized from methanol and acetone, respectively. **2a**: yield 0.04 g (20%); decomposes at 175 °C (under argon); MS: *m/z* 383 ($M^{\oplus}$) relative to ^{184}W. — **3a**, **b**: yield 0.11 g (52%); decomposes at 105–108 °C (under argon); MS: *m/z* 412 ($M^{\oplus}$) relative to ^{184}W.

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1, 87862-56-4; **2a**, 92184-47-9; **2b**, 92184-48-0; **3a**, 92144-51-9; **3b**, 92218-52-5; **3c**, 92144-52-0

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Spherical Host Molecules for the Complexation of Aromatic Hydrocarbons in Aqueous Solution

By *François Diederich** and *Klaus Dick*

We have recently reported on 1 : 1 inclusion complexes of a flat cyclophane-like host molecule with aromatic hy-

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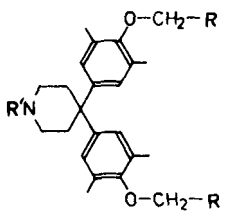
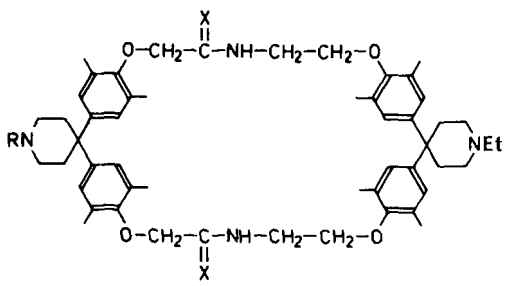
drocarbons in aqueous solution[1]. The properties of the complexes of spherical host molecules with anionic or cationic guests[2] stimulated us to prepare spherical, water-soluble macrocycles with an apolar cavity of defined size which complexes neutral arenes in aqueous solution.

The synthesis of the precursors **3**, **5**, and **7** necessary for the cyclization steps starts from *N*-acetyl-4,4-bis(3,5-dimethyl-4-hydroxyphenyl)piperidine[1a,b]. Reaction with ethyl bromoacetate afforded the diester **1** (KOH, tetrahydrofuran (THF); 67%; m.p. 108—109 °C)[3], which was hydrolyzed to give the dicarboxylic acid **2** (K_2CO_3, EtOH/H_2O; 98%; m.p. 236 °C)[3]. For the preparation of the bis(*N*-hydroxysuccinimide ester) **3** as activated carboxylic acid component for the amide-cyclization to give **8**, **2** was allowed to react with *N*-hydroxysuccinimide (dicyclohexylcarbodiimide, dioxane; 84%; m.p. 156 °C)[3,4]. Passage of ammonia into the reaction solution of **3** led to formation of the triamide **4** (84%; m.p. 240—241 °C)[3], which was reduced to the cyclization component **5** (B_2H_6, THF; colorless glass; 96%)[3]. **3** reacts with **5** to give the macrocycle **8** (CH_2Cl_2, 0 °C, dilution principle; 41%; m.p. > 335 °C, decomp.)[3], which on reduction yielded the cyclic precursor **9** for the cyclization to the macrobicycle (B_2H_6, THF; 96%; m.p. 240—241 °C)[3].

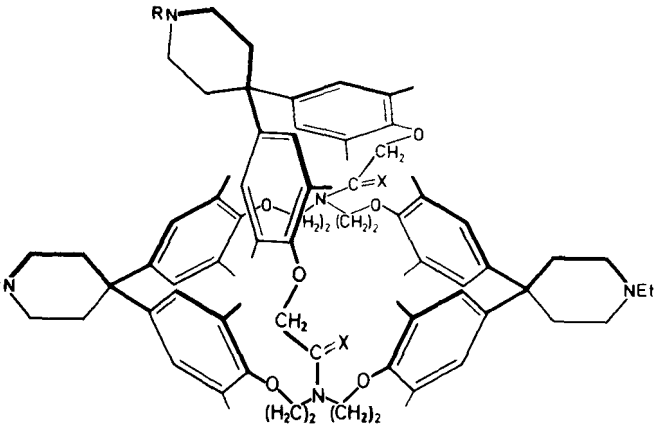


	R	R'
1	EtO–CO	Ac
2	HO–CO	Ac
3	succinimido-O–CO	Ac
4	H_2N–CO	Ac
5	H_2N–CH_2	Et
6	HO–CO	$PhCH_2O$–CO
7	Cl–CO	$PhCH_2O$–CO



8, R = Ac, X = O
9, R = Et, X = 2H

For the preparation of the second component **7** necessary for the cyclization, **1** was hydrolyzed (2 N NaOH, 6 h, 100 °C), and the crude product was allowed to react with benzyl chloroformate to give the dicarboxylic acid **6** (92%; m.p. 95 °C decomp.)[3]. The dichloride **7** obtained by reaction of **6** with sulfinyl chloride in benzene was then cyclized, without further purification, with **9** to give the macrobicycle **10**, [toluene, 0 °C, dilution principle; 38%; m.p. 189 °C, decomp.; FAB-MS[5]: *m/z* 1385 [100%, ($M^{\oplus}$ + H)], 929 (37), 693 (30), 553 (24), 465 (55)]. Catalytic cleavage of the amine-protecting group furnished **11** [H_2/Pd (10%), EtOH, 98%; m.p. 185 °C][3]; reductive alkylation of **11** yielded the host molecule **12** (CH_3COOH, $NaBH_4$, 55 °C, 12 h; 55%; m.p. 180 °C)[3]. **11** was acetylated to give **13** (Ac_2O; 85%; m.p. 200 °C)[3], which could be reduced to the host molecule **14** (B_2H_6, THF; 79%; m.p. 146 °C). Alternatively, **14** could be prepared by reduction of **12** (B_2H_6, THF; 83%). The simple 360-MHz ^{1}H-NMR spectrum reflects the higher symmetry (D_{3h}) of the macrobicycle **14** compared to **10**—**13**[3].



	R	X		R	X
10	$PhCH_2O$–CO	O	**13**	Ac	O
11	H	O	**14**	Et	2H
12	Et	O			

12 and **14** are readily soluble in aqueous solution at pH < 5. Their ^{1}H-NMR spectra [360 MHz, 303 K, 0.5 M solution of KD_2PO_4 in D_2O, pD 4.3, sodium 2,2,3,3-tetradeuterio-3-(trimethylsilyl)propionate (TSP) ext.] show concentration-independent shifts at [**12**] < 10^{-3} mol·L^{-1} and [**14**] < 5×10^{-3} mol·L^{-1}. All complexation experiments in aqueous solution were carried out at pH < 5 and [host] < 10^{-3} mol·L^{-1}.

In weakly acid solution, **12** contains a predominately apolar cavity, since the protonated amine nitrogen atoms are directed outwards. **12** is therefore a very good host for appropriately sized neutral arenes. With [**12**] = 5.0×10^{-4} mol·L^{-1} in a 0.5 M aqueous solution of KH_2PO_4, a $\approx 2.3 \times 10^{-4}$ M aqueous solution of pyrene was obtained by solid-liquid extraction[1a,b]. Using the maximum solubility of pyrene in such a solution in the absence of **12** (2.0×10^{-7} mol·L^{-1}), the association constant K_a of the 1:1 complex could be calculated to be $K_a = (4.1 \pm 0.5) \times 10^6$ L·mol^{-1} (293—295 K)[1b]. For the 1:1 complex of the recently described flat macrocyclic host molecule with pyrene in D_2O (293—295 K) a value of $K_a = 1.1 \times 10^6$ L·mol^{-1} was found[1b]. For the **12**-naphthalene complex, $K_a = (1.2 \pm 0.2) \times 10^4$ L·mol^{-1} was obtained. The complexation between **12** and arenes is virtually independent of the nature of the inorganic ions present in the solution up to ionic strengths of 1 mol·L^{-1}. The ^{1}H-NMR spectrum (for conditions, see above) demonstrates the strong complexation between **12** and pyrene. The exchange between host and guest is slow: In the ^{1}H-NMR spectrum of the solution with [**12**] = 5×10^{-4} mol·L^{-1} and [pyrene] = 2.3×10^{-4} mol·L^{-1}, signals of the free and complexed host are present in an intensity ratio $\approx 2.7 : 2.3$

along with the signals of the complexed pyrene. The pyrene lies in the plane of **12** which runs through the three spiro carbon atoms. This orientation, which naphthalene also assumes (NMR), is supported by the large upfield shift of the signals of the pyrene protons in the complex solution (H1: $\Delta\delta = +2.04$, H2: $+1.03$[7], H4: $+1.99$), the upfield shift of the resonances of the protons of the host molecule **12** which lie about perpendicular to this plane ($O-CH_2-CH_2-N-C(O)-CH_2-O$), and the downfield shift of the signals of the protons of **12** in this plane (e.g. aryl-*H*).

The two protonated amine nitrogen atoms in the cavity of **14** in weakly acid solutions, on the other hand, considerably reduce the hydrophobic character of this cavity. The complexation of arenes is weaker: With a 0.5 M aqueous KH_2PO_4 solution ($[\mathbf{14}] = 5.0 \times 10^{-4}$ mol·L^{-1}), only a $\approx 2.3 \times 10^{-6}$ M solution of pyrene was obtained by solid-liquid extraction. With 0.1 M aqueous hydrochloric acid ($[\mathbf{14}] = 5 \times 10^{-4}$ mol·L^{-1}), the extraction by complexation is even weaker. That the weak complexation of arenes is due to the two protonated nitrogen atoms in the cavity of **14** and not to geometric factors is supported by the observation that the complexation between pyrene and non-protonated host **14** in methanol is surprisingly strong. In the ^{1}H-NMR spectrum (360 MHz, 303 K, [D$_4$]methanol, TSP ext., $[\mathbf{14}] = 6 \times 10^{-3}$ mol·L^{-1}, [pyrene] $= 3 \times 10^{-3}$ mol·L^{-1}) the signals of the pyrene protons are shifted upfield very strongly (H1: $\Delta\delta = +1.77$, H2: $+1.19$, H4: $+1.97$). This upfield shift as well as specific upfield and downfield shifts of the signals of host protons in the complex solution indicate that pyrene is located similarly as in the cavity of **12**. The very different complexing behavior of **12** and **14** towards arenes in aqueous solution underscores the significance of the outward directing ionic groups responsible for promoting solubility in water.

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[1] a) F. Diederich, K. Dick, *Angew. Chem. 95* (1983) 730; *Angew. Chem. Int. Ed. Engl. 22* (1983) 715; *Angew. Chem. Suppl. 1983*, 957; b) *J. Am. Chem. Soc.*, in press; c) F. Diederich, D. Griebel, *ibid.*, in press.

[2] a) J.-M. Lehn, *Acc. Chem. Res. 11* (1978) 49; b) F. P. Schmidtchen, *Angew. Chem. 89* (1977) 751; *Angew. Chem. Int. Ed. Engl. 16* (1977) 720; *Chem. Ber. 114* (1981) 597; c) cf. also S. P. Miller, H. W. Whitlock, Jr., *J. Am. Chem. Soc. 106* (1984) 1492; d) cf. also F. Vögtle, H. Sieger, W. M. Müller, *Top. Curr. Chem. 98* (1981) 107; e) cf. also D. J. Cram, *Science 219* (1983) 1177.

[3] Elemental analyses and spectroscopic data are consistent with the proposed structures.—**8**: EI-MS: *m/z* (*M*$^\oplus$) 886; ^{1}H-NMR (360 MHz, [D$_6$]dimethyl sulfoxide (DMSO), 393 K): $\delta = 0.94$ (t, $J = 7.1$ Hz, 3H), 1.95 (s, 3H), 2.12 (s, 12H), 2.13 (s, 12H), 2.25 (q, $J = 7.1$ Hz, 2H), 2.2—2.35 (m, 8H), 2.35—2.45 (m, 4H), 3.4—3.5 (m, 4H), 3.55 (q, $J = 5.7$ Hz, 4H), 3.85 (t, $J = 5.7$ Hz, 4H), 4.23 (s, 4H), 6.83 (s, 4H), 6.84 (s, 4H), 7.52 (t, $J \approx 5.7$ Hz, 2H).—**12**: FAB-MS [5]: *m/z* 1279 [29%, (*M*$^\oplus$ + H)], 929 (100), 465 (70); ^{1}H-NMR (360 MHz, [D$_6$]DMSO, 393 K): $\delta = 0.93$ (t, $J = 7.1$ Hz, 6H), 0.94 (t, $J = 7.1$ Hz, 3H), 2.01 (s, 24H), 2.10 (s, 12H), 2.23 (q, $J = 7.1$ Hz, 6H), 2.2—2.35 (m, 12H), 2.35—2.5 (m, 12H), 3.15—3.3 (m, 4H), 3.6—3.75 (m, 4H), 3.75—3.9 (m, 4H), 3.9—4.1 (m, 4H), 4.51 (s, 4H), 6.78 (s, 8H), 6.80 (s, 4H).—**14**: FAB-MS [5]: *m/z* 1251 [100%, (*M*$^\oplus$ + H)], 627 (63), 553 (35), 461 (56); ^{1}H-NMR (360 MHz, $CDCl_3$, 303 K): $\delta = 1.04$ (t, $J = 7.1$ Hz, 9H), 2.12 (s, 36H), 2.32 (q, $J = 7.1$ Hz, 6H), 2.25—2.4 (m, 12H), 2.4—2.55 (m, 12H), 3.01 (t, $J = 6.8$ Hz, 12H), 3.61 (t, $J = 6.8$ Hz, 12H), 6.72 (s, 12H).

[4] G. W. Anderson, J. E. Zimmerman, F. M. Callahan, *J. Am. Chem. Soc. 86* (1964) 1839.

[5] We thank Prof. Dr. *H. Schwarz*, Berlin, and Dr. *L. Grotjahn*, Braunschweig, for recording the FAB mass spectra.

[6] G. W. Gribble, J. M. Jasinski, J. T. Pellicone, J. A. Panetta, *Synthesis 1978*, 766.

[7] The triplet of H2 is only visible at 353 K when the exchange between host and guest is rapid; the quoted upfield shift was measured at this temperature.

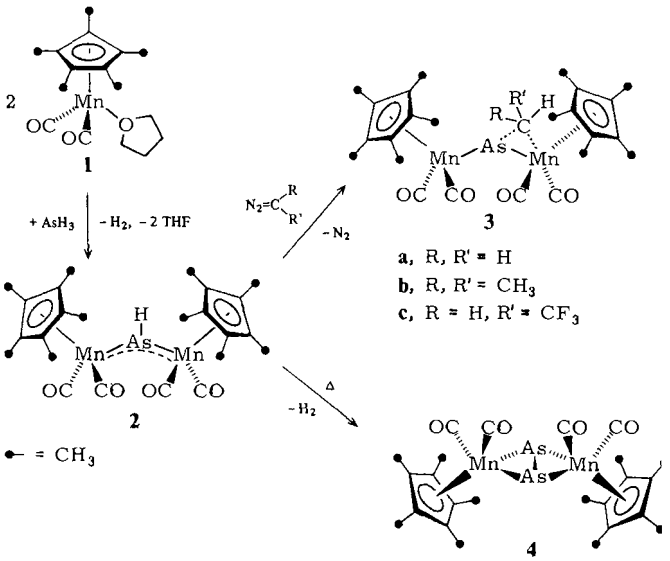
[8] F. Diederich, K. Dick, *Tetrahedron Lett. 23* (1982) 3167.

Arsanediyl (Arsinidene) and Diarsene Complexes by Metal-Induced Degradation of Monoarsane**

By *Wolfgang A. Herrmann**, *Basile Koumbouris*, *Thomas Zahn*, and *Manfred L. Ziegler*

Dedicated to Professor Margot Becke on the occasion of her 70th birthday

Complexes exhibiting multiple bonds between transition metals and ligand-free ("naked") main group elements are highly reactive[1]. They add smoothly, for example, to small, unsaturated species such as the methylene fragment[2]. For the systematic introduction of bare main group elements into organometallic complexes not only the elements themselves, but also their binary hydrides appear promising reagents. Following the recently reported use of GeH_4[2] and TeH_2[3] in the synthesis of unusual multinuclear germanium and tellurium complexes, respectively, we have now, for the first time, successfully synthesized arsanediyl (arsinidene) and diarsene complexes using monoarsane.



Although the coordination chemistry of monoarsane appeared to have already been basically investigated[4], we treated this reactive compound with the solvent complex **1** at room temperature and obtained the deep-blue, extremely air-sensitive binuclear complex **2** (ca. 80%)[5]. According to the NMR spectra and the results of a single-crystal X-ray structure analysis (Fig. 1), the basic skeleton of **2** contains, for the first time, the arsanediyl ligand, AsH, in a symmetrical bridging position. Substituted derivatives exhibiting AsR groups (R = alkyl, phenyl, halogen) have been known for some time from the work of *Huttner* et

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[**] Multiple Bonds between Main Group Elements and Transition Metals, Part 11. This work was supported by the Deutsche Forschungsgemeinschaft, the Herbert-Quandt-Stiftung of Varta Batterie AG, Hoechst AG, and the Bundesministerium für Forschung und Technologie.—Part 10: W. A. Herrmann, C. Hecht, M. L. Ziegler, T. Zahn, *J. Organomet. Chem.*, in press.

al.[6]. As in these latter complexes, the arsanediyl bridge in **2** is bonded to both manganese atoms via two very short bonds, resulting in a three-center, four-electron bonding system (Mn–As 224.7(1) pm; Mn–As–Mn′ 139.3(1)°). In solution, **2** forms a mixture of rotamers (IR), whose components rapidly interconvert on the NMR time scale.

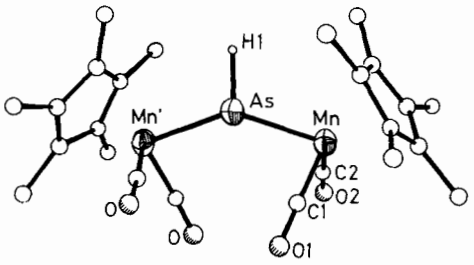
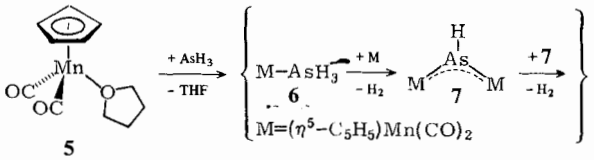


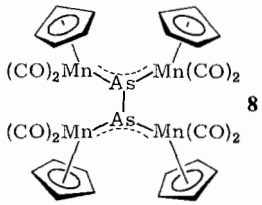
Fig. 1. Molecular structure of **2** in the crystal. Space group Fdd2-C_{2v}^{19}, $Z=8$, $a=804.8(2)$, $b=1559.7(3)$, $c=4167.0(8)$ pm; $R_{iso}=0.092$, $R_{aniso}=0.039$, $R_w=0.034$.—Selected distances [pm] and angles [°]: Mn–As 224.7(1), Mn–C1 173.7(8), Mn–C2 172.6(9), C1–O1 116.1(10), C2–O2 116.9(11); Mn–As–Mn′ 139.3(1), As–Mn–C1 89.1(2), Mn–C1–O1 177.3(7), Mn–C2–O2 176.9(6).

The AsH bridge in **2** can be functionalized: thus, at −80°C diazoalkanes undergo carbene insertion within seconds to afford almost quantitatively the unsymmetrical derivatives **3**, in which one of the two As–Mn bonds is probably bridged by an alkyl group[5,7]. Furthermore, clean cleavage of the As–H bond is achieved upon solid-state thermolysis of the pure arsinidine complex **2** at 120–140°C in vacuo. The novel Mn_2As_2 complex **4** thus formed in >85% yield is surprisingly thermally stable up to above 250°C; according to a single-crystal X-ray structure analysis it does not have the expected tetrahedrane- but rather a "butterfly"-skeleton (Fig. 2)[5] with the two As_2Mn triangles forming an interplanar angle of 121.8°. Whereas the Mn–Mn distance (402 pm) is too large for a bonding interaction[8], the extremely short As–As bond (222.5 pm) exhibits considerable multiple bond character (As–As single bonds 243–246, double bonds ca. 222 pm[9]). The Mn–As bonds (251–257 pm) are much longer than in the μ-arsanediyl complex **2** and therefore can be interpreted as single bonds. Mn_2As_2 complexes (M = Mo, W) having tetrahedrane-type structures have recently been synthesized in low yields[10]; the As–As bonds in these cases are significantly longer than in **4** (231–232 pm[10]), but are, nevertheless, formally double bonds.

The stepwise metal-induced degradation of arsane via AsH- to As_2-complexes with concomitant elimination of hydrogen (GC) as observed for the first time with the reaction sequence **1** → **2** → **4** occasioned the investigation of the reported reaction of the solvent complex **5** with monoarsane from which the extremely thermolabile complex **6** had been isolated in 1.5% yield by *Fischer* et al.[4a]. We were able to detect **6** in the product mixture (IR, MS), but it appeared only to be an intermediate: in >80% yield, the major product formed is the tetranuclear μ-diarsane complex **8**[5,11], which results formally from the coupling of two arsanediyl complexes **7** by elimination of H_2; once again, this reaction reflects the lability of the As–H bonds. Because of the bulky pentamethylcyclopentadienyl ligands, **2** does not undergo this type of coupling reaction.



5



8

From the reactions described here, the instability of AsH_3 complexes[4] appears to be kinetic in nature and to involve spontaneous elimination of H_2, which the metal-arsenic bonds initially leave intact. The reactive AsH bridge in **2** facilitates both carbene insertions and intermolecular As–As couplings. The readily accessible monoarsane is hence a suitable precursor for organometallic complexes containing AsH or unsubstituted (bare) As_x skeletal building blocks.

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CAS Registry numbers:
1, 86155-78-4; **2**, 92396-58-2; **3a**, 92396-59-3; **3b**, 92396-60-6; **3c**, 92396-61-7; **4**, 92366-17-1; **5**, 12093-26-4; **6**, 33292-28-3; **8**, 92270-27-4; AsH_3, 7784-42-1; $N_2=CH_2$, 334-88-3; $N_2=C(CH_3)_2$, 2684-60-8; $N_2=CHCF_3$, 371-67-5; As, 7440-38-2; Mn, 7439-96-5

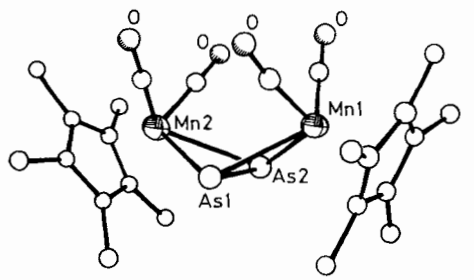


Fig. 2. Molecular structure of **4** in the crystal. Space group $P2_1/n$, $Z=4$, $a=818.9(2)$, $b=1495.1(3)$, $c=2132.1(4)$ pm, $\beta=98.6°$; $R_{aniso}=0.046$, $R_w=0.037$. Selected distances [pm] and angles [°]: As–As 222.5(1), Mn–As 254.5 (average), Mn–CO 178.2 (average), C–O 115.9 (average); Mn1–As1–Mn2 103.2(1), Mn1–As2–Mn2 104.5(1).

[1] Short summary: W. A. Herrmann in B. L. Shapiro: *Organometallic Compounds—Synthesis, Structure, and Theory, Vol. 1*, Texas A & M University Press, College Station, TX, USA 1983, p. 383.

[2] W. A. Herrmann, J. Weichmann, U. Küsthardt, A. Schäfer, R. Hörlein, C. Hecht, E. Voss, R. Serrano, *Angew. Chem. 95* (1983) 1019; *Angew. Chem. Int. Ed. Engl. 22* (1983) 979; *Angew. Chem. Suppl. 1983*, 1543.

[3] a) M. Herberhold, D. Reiner, D. Neugebauer, *Angew. Chem. 95* (1983) 46; *Angew. Chem. Int. Ed. Engl. 22* (1983) 59; *Angew. Chem. Suppl. 1983*, 10; b) W. A. Herrmann, C. Hecht, M. L. Ziegler, B. Balbach, *J. Chem. Soc. Chem. Commun. 1984*, 686.

[4] Previous complexes of monoarsane: a) E. O. Fischer, W. Bathelt, M. Herberhold, J. Müller, *Angew. Chem. 80* (1968) 625; *Angew. Chem. Int. Ed. Engl. 7* (1968) 634; b) E. O. Fischer, W. Bathelt, J. Müller, *Chem. Ber. 103* (1970) 1815.

[5] Correct elemental analyses and osmometric molecular weight determinations were obtained for the new complexes **2**, **3a**–**c**, **4**, and **8**; these compounds were synthesized, purified, and manipulated by use of Schlenk, vacuum-line, and glove-box techniques.—a) *(μ-Arsanediyl)bis[dicarbonyl(η⁵-pentamethylcyclopentadienyl)manganese]* **2**: Black crystals, m.p. = 173°C (decomp.). ^{1}H-NMR ($CDCl_3$, 25°C): δ(CH_3) 1.77 (s, 30H), δ(AsH) 15.08 (s, 1H). IR (KBr, ν(CO) [cm^{-1}]): 1960 s, 1915 s, 1896 s; (*n*-hexane): 1983 s, 1960 w, 1930 vs, 1908 s, 1884 s. FD-MS: *m/z* 568 ($M^{\oplus}$; at >10 mA filament heating; the parent ion of **4** with *m/z* 642

is also observed). EI mass spectra (Varian MAT CH 7; $T_Q \leq 120°C$): *m/z* 568 ($M^{\oplus}$ of **2** and fragmentation pattern; at higher T_Q $M^{\oplus}$ of **4** and fragmentation are observed.—b) *(μ,η²-diarsene)bis[dicarbonyl(η⁵-pentamethylcyclopentadienyl)manganese]* **4**: red-brown crystals, m.p. = 238°C (decomp.). ^{1}H-NMR (C_6D_6, 25°C): $\delta(CH_3)$ 1.54 (s). IR (KBr, ν(CO) [cm^{-1}]): 1963 vs, 1920 sh, 1910 s, 1880 sh; (THF) 1972 vs, 1918 s. EI-MS (70 eV): *m/z* 642 ($M^{\oplus}$).—c) *Bis[(μ-arsene)bis[dicarbonyl(η⁵-cyclopentadienyl)manganese]](As–As)* **8**: violet crystals, m.p. = 218°C (decomp.). ^{1}H-NMR ($CDCl_3$, 25°C): $\delta(C_5H_5)$ 4.85 (s). IR (THF, ν(CO) [cm^{-1}]): 1980 vs, 1935 s; (KBr) 1970 s, 1930 vs, 1910 s. FD-MS: *m/z* 854 ($M^{\oplus}$), in addition *m/z* 427 corresponding to $[Cp_2Mn_2(CO)_4As]^{\oplus}$).

[6] Selected examples: a) G. Huttner, H.-G. Schmid, *Angew. Chem. 87* (1975) 454; *Angew. Chem. Int. Ed. Engl. 14* (1975) 433; b) J. von Seyerl, U. Moering, A. Wagner, A. Frank, G. Huttner, *ibid. 90* (1978) 912 and *17* (1978) 844, resp.; c) J. von Seyerl, B. Sigwarth, H.-G. Schmid, G. Mohr, A. Frank, M. Marsili, G. Huttner, *Chem. Ber. 114* (1981) 1392; d) G. Huttner, B. Sigwarth, J. von Seyerl, L. Zsolnai, *ibid. 115* (1982) 2035 (trigonal-planar coordinated arsenic).

[7] Example: (μ,η²-Isopropylarsanediyl)bis[dicarbonyl(η⁵-pentamethylcyclopentadienyl)manganese] **3b**: orange air-stable lamina, decomp. 130°C. ^{1}H-NMR (CD_2Cl_2, 25°C): $\delta(C_5Me_5)$ 1.85, 1.77 [2s, each 15H], $\delta(CMe_2)$ 1.54 (br.), CH not observed. IR (Et_2O, ν(CO) [cm^{-1}]): 1950 s, 1905 vs, 1895 sh, 1850 s; (KBr) 1957 s, 1915 vs, 1895 m, 1855 s. FD-MS: *m/z* 610 ($M^{\oplus}$). ^{13}C-NMR ($CDCl_3$, 25°C): $\delta(C_5Me_5)$ 91.47, 96.23; $\delta(C_5(CH_3)_5)$ 9.99, 10.37; $\delta(C(CH_3)_2)$ 31.69, 32.75, $\delta(CMe_2)$ 69.90; δ(CO) 226.26, 234.11, 235.33, 236.38.

[8] Mn–Mn bonds are shorter than approx. 320 pm; cf. I. Bernal, M. Creswick, W. A. Herrmann, *Z. Naturforsch. B 34* (1979) 1354.

[9] a) A. H. Cowley, J. G. Lasch, N. C. Norman, M. Pakulski, *Angew. Chem. 95* (1983) 1019; *Angew. Chem. Int. Ed. Engl. 22* (1983) 978; *Angew. Chem. Suppl. 1983*, 1493; b) B. Sigwarth, L. Zsolnai, H. Berke, G. Huttner, *J. Organomet. Chem. 226* (1982) C5.

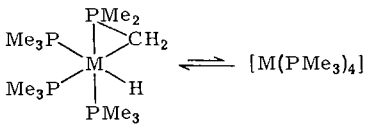
[10] P. Sullivan, A. L. Rheingold, *Organometallics 1* (1982) 1547.

[11] Compound **8** can be prepared from the corresponding μ-chloroarsanediyl complex by reductive AsAs-coupling with zinc dust; a single-crystal X-ray structure analysis is consistent with our proposed structure: B. Sigwarth, Ph.D. Thesis, Universität Konstanz, Germany 1983.

$(PMe_3)_3MS_7$ (M = Ru, Os): The First Polysulfido Metal Complexes with a Tridentate $S_n^{2\ominus}$ Ligand**

By *Josef Gotzig, Arnold L. Rheingold,* and *Helmut Werner**

In contrast to the pentacarbonyl complexes $M(CO)_5$, analogous pentakis(trimethylphosphane)metal complexes $M(PMe_3)_5$ (M = Fe, Ru, Os) are unknown. During attempts to prepare these complexes, compounds **1** were obtained. In the solid state **1** has a structure in which three PMe_3 groups and an H atom are bonded to the metal M of a phosphametallacyclopropane ring; M is therefore octahedrally coordinated[1]. In solution, the complexes exist in equilibrium with the corresponding coordinatively unsaturated isomers; however, the position of the equilibrium lies mainly to the side of the phosphametallacyclopropanes.

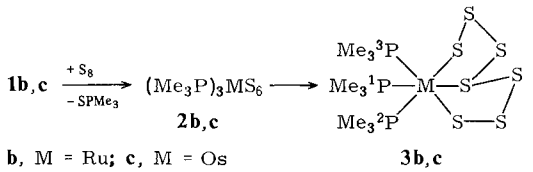


1

a, M = Fe; **b**, M = Ru; **c**, M = Os

The chemistry of the complexes **1** is dominated by their enhanced reactivity towards electrophiles. Whereas the constitution of the products formed in the reactions of **1a** indicate that *both* isomers present in the equilibrium react[2], similar evidence is lacking for **1b**, **c**[1b,c]. It was our aim to find such evidence by studying the reaction of **1b**, **c** with sulfur, since it is known that the 16-electron complexes $[C_5H_5M(PR_3)]$ (M = Co, Rh; R = Me, Ph) prepared in situ, which are comparable to the coordinatively unsaturated $[M(PMe_3)_4]$, can be trapped by S_8 to form the thiametallacycles $C_5H_5(PR_3)MS_5$[3].

If a solution of **1b** or **1c** is therefore treated with S_8 in the molar ratio 1:5/8, the starting material is not completely consumed. Only when the reactants are mixed in the molar ratio 1:1 does the reaction go to completion to yield $SPMe_3$ (NMR) and a dark precipitate which is insoluble in benzene. After chromatography[4a], *dark brown*, air-stable solids **2b**, **c** are isolated[4b].



Attempts to prepare single crystals of **2b**, **c** led to an unexpected result. Slow diffusion of hexane in solutions of **2b** and **2c** in acetone affords *orange-red* crystals which are not identical with the dissolved compound. According to elemental analysis, the ratio M:S = 1:7[4b]. In the NMR spectra, however, there is no detectable difference between **2b**, **c** and **3b**, **c**. Thus, in the ^{1}H- and in the ^{31}P-NMR spectra two types of CH_3 protons and phosphorus nuclei are observed, the latter forming an AB_2 spin pattern[5]. At present, no conclusive statement can be made about the mechanism of formation of **3** from **2**. A more detailed investigation of the *clear* solution (from which the crystals precipitate) is planned as soon as larger quantities of the starting material are available.

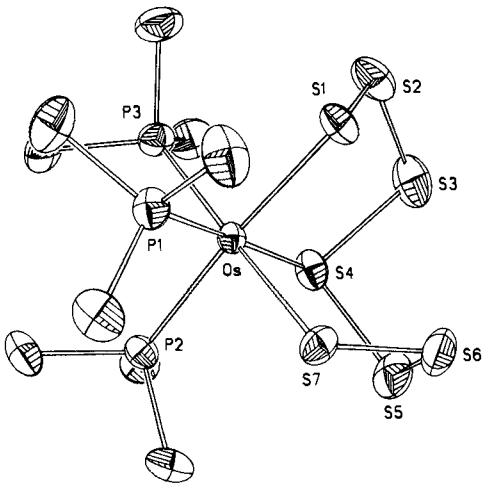


Fig. 1. Crystal structure of **3c**. Selected bond lengths [pm] and bond angles [°]: Os-P1 236.4(2), Os-P2 234.4(2), Os-P3 233.8(2), Os-S1 243.2(2), Os-S4 231.0(2), Os-S7 243.9(2), S1-S2 203.6(3), S2-S3 201.9(4), S3-S4 220.5(3), S4-S5 215.0(3), S5-S6 201.0(3), S6-S7 204.4(4), P1-Os-P2 94.6(1), P1-Os-P3 96.4(1), P2-Os-P3 92.3(1), P1-Os-S1 85.9(1), P2-Os-S1 174.9(1), P3-Os-S1 92.7(1), P1-Os-S4 173.3(1), P2-Os-S4 87.2(1), P3-Os-S4 90.0(1), P1-Os-S7 81.1(1), P2-Os-S7 90.0(1), P3-Os-S7 176.7(1), S1-Os-S4 91.7(1), S1-Os-S7 85.0(1), S4-Os-S7 92.5(1).

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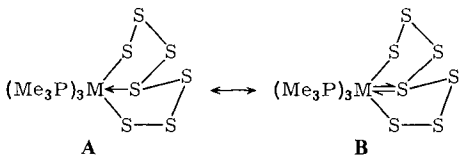
[**] This work was supported by the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie, and by gifts of chemicals from Degussa AG.

The molecular structure of the osmium complex **3c** was determined by X-ray structural analysis (Fig. 1)[6]. The $S_7^{2\ominus}$ unit is linked via S1, S4, and S7 to Os, which attains the preferred octahedral coordination for oxidation state +2. As far as the structural data are concerned, special attention is drawn to the different Os–S and S–S bond lengths. Compared to Os-S1 and Os-S7, the significantly shorter Os-S4 distance indicates that in addition to the donor bond from S4 to the Os atom an acceptor bond may be present, i.e., not only **A** but also the resonance structure **B** must be considered in a description of the bonding in **3b, c**. The unique role of S4 in the OsS_7 bicyclic system can also be seen in the larger Os-P1 bond (*trans* to S4) and in the elongation of the S3-S4 and S4-S5 bonds.



A **B**

To the best of our knowledge, **3b, c** are the first metal complexes in which an MS_7 unit is present and an $S_7^{2\ominus}$ ion is coordinated as a *tri*dentate ligand. Recently, monocyclic MS_n ring systems with $n = 6$[7a] and $n = 9$[7b] have been prepared with M = Cu or Au and their structures characterized. It seems interesting that the bicyclic OsS_7 moiety has the same "paddle-wheel"-like *exo/endo*-conformation as the $S_8^{2\oplus}$ ion in $S_8(AsF_6)_2$[8].

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CAS Registry numbers:
1b, 78789-89-6; **1c**, 84108-58-7; **2b**, 92346-64-0; **2c**, 92346-65-1; **3b**, 92346-66-2; **3c**, 92346-67-3

[1] a) M = Fe: H. H. Karsch, H.-F. Klein, H. Schmidbaur, *Angew. Chem. 87* (1975) 630; *Angew. Chem. Int. Ed. Engl. 14* (1975) 637; J. W. Rathke, E. L. Muetterties, *J. Am. Chem. Soc. 97* (1975) 3272; b) M = Ru: H. Werner, R. Werner, *J. Organomet. Chem. 209* (1981) C60; c) M = Os: H. Werner, J. Gotzig, *Organometallics 3* (1983) 547.

[2] H. H. Karsch, H.-F. Klein, H. Schmidbaur, *Chem. Ber. 110* (1977) 2200; H. H. Karsch, *ibid. 110* (1977) 2213, 2699; *111* (1978) 1650.

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[4] a) Experimental procedure: A solution of **1b** (**1c**) (0.34 mmol) in 5 mL benzene is treated with S_8 (87 mg, 0.34 mmol) and stirred for 1 h. The solution becomes warm and a dark oily precipitate is formed. After decanting off the solution, the precipitate is washed with hexane (3 × 5 mL), dried, dissolved in 2 mL CH_2Cl_2, and chromatographed on silica gel (Ru) or Al_2O_3 (Woelm, activity III) (Os). Addition of hexane to the concentrated solution (ca. 2 mL) gives a dark brown crystalline solid which is repeatedly washed with hexane and dried in vacuo. Yield 64% **2b** (67%, **2c**); m.p. = 93 °C, dec. (147 °C, dec.). After dissolving **2b, c** in acetone and covering with hexane, orange-red crystals are formed; m.p. = 137 °C, dec. (**3b**) (161 °C, dec., (**3c**)).—b) The sulfur content is particularly different for **2b, c** and **3b, c**. **2b**: calc. 36.96, found 37.01; **2c**: calc. 31.50, found 31.62; **3b**: calc. 40.53, found 40.32; **3c**: calc. 34.91, found 34.82%.

[5] a) ^{1}H-NMR (60 MHz, 25 °C, CH_2Cl_2, int. TMS). **2b, 3b**: $\delta(P^1Me_3) = 1.74$ (d, $J(PH) = 8.5$ Hz), $\delta(P^{2,3}Me_3) = 1.39$ (vt, $N = 7.5$ Hz); **2c, 3c**: $\delta(P^1Me_3) = 1.89$ (d, $J(PH) = 8.5$ Hz), $\delta(P^{2,3}Me_3) = 1.50$ (vt, $N = 8.1$ Hz).—b) ^{31}P-NMR (90 MHz, 25 °C, $CDCl_3$, ext. 85% H_3PO_4). **2b, 3b**: $\delta(P^1) = -5.99$, $\delta(P^{2,3}) = -9.05$, $J(P^1P^{2,3}) = 32.8$ Hz; **2c, 3c**: $\delta(P^1) = -50.86$, $\delta(P^{2,3}) = -52.86$, $J(P^1P^{2,3}) = 22.8$ Hz.

[6] Monoclinic, space group $P2_1/n$, $Z = 4$, $a = 938.4(3)$, $b = 1487.3(4)$, $c = 1562.3(5)$ pm, $\beta = 98.81(2)°$; $V = 2154.6 \times 10^6$ pm^3. $Mo_{K\alpha}$ ($\lambda = 71.073$ pm); $4° \leq 2\theta \leq 50°$ (Nicolet P3); 3376 independent reflections with $F_0 \geq 3\sigma(F_0)$; $R_{iso} = 0.0416$, $R_{aniso} = 0.0333$. Further details of the crystal structure determination can be obtained from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen by qouting the depository number CSD 50982, the names of the authors and the journal citation.

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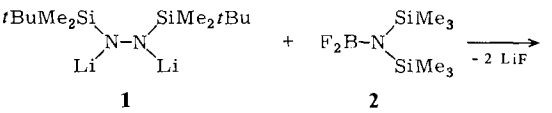
Diazaboracyclopropane**

By *Uwe Klingebiel**

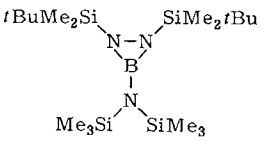
Strained boron-phosphorus[1–3] and boron-carbon[4–6] three-membered ring systems have been synthesized in the last ten years by several groups. Among the thoroughly studied boron-nitrogen heterocycles[7,8], no strained BN_2-ring compound was previously known.

Like dihalosilanes[8,9], dihaloboranes[8,10] react with lithiated hydrazines to afford, preferentially, six-membered rings. The synthesis of an SiN_2 three-membered ring using the bulky di-*tert*-butyldifluorosilane was recently reported. Preparation of a BN_2 three-membered ring should also be favored by the presence of sterically demanding substituents on the nitrogen and boron atoms.

As expected, reaction of the doubly lithiated *N,N'*-bis(*tert*-butyldimethylsilyl)hydrazine **1** with difluorobis(trimethylsilyl)aminoborane **2** leads to the diazaboracyclopropane 1,2-bis(*tert*-butyldimethylsilyl)-3-[bis(trimethylsilyl)amino]diazaboriridine) **3**.



1 **2**



3

The structure of the BN_2 ring system was elucidated by CH elemental analysis and by cryoscopic determination of the molecular mass in cyclohexane ($M_r = 432$); the presence of a dimer, i.e. a B_2N_4 ring system[10], can therefore be excluded also in solution. Since it has not yet proved possible to isolate single crystals suitable for an X-ray structure investigation, the configuration assigned to this three-membered ring is corroborated by NMR data. The ^{11}B-NMR shift ($\delta = 27.2$) occurs in the region associated with sp^2-hybridized boron. The nitrogen is—in part, certainly because of the bonded silyl groups—sp^2-hybridized; the ^{14}N-NMR shift is observed at $\delta = -329$ (rel. CH_3NO_2). The sharp ^{1}H- and ^{13}C-NMR signals indicate the presence of equivalent substituents in the ring plane. The ^{29}Si-NMR signals occur in the region expected.

Hence, the NMR data for this silyl- and silylamine-substituted three-membered ring differ also from those of the recently synthesized BN_2 ring which bears isopropyl groups at the nitrogen.

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Procedure

A solution of **1** (0.05 mol) in 200 mL *n*-hexane is cooled to −30°C and to this is added over 4 h, with constant stirring, a solution of **2** (0.05 mol) in 150 mL *n*-hexane. After being warmed up to room temperature, precipitated LiF is centrifuged off. The solvent is removed using an oil pump and **3**, which precipitates out even at this stage, is purified by dissolution in a little *n*-hexane at room temperature and precipitation at −30°C. Yield: 10.5 g (85%); Fp = 69°C; MS (70 eV): *m/z* 429 (15) $M^{\oplus}$ (with theoretical B-isotope abundance), 414 (5) ($M^{\oplus} - CH_3$), 372 (100) ($M^{\oplus} - C_4H_9$); ^{1}H-NMR (CH_2Cl_2, TMS int.): $\delta = 0.10$ ($SiMe_2$), 0.26 ($SiMe_3$), 0.97 (CMe_3); ^{11}B-NMR (CH_2Cl_2/C_6D_6, $BF_3 \cdot OEt_2$ ext.): $\delta = 27.2$; ^{13}C-NMR (CH_2Cl_2/C_6D_6, TMS int.): $\delta = -3.34$ ($SiMe_2$), 3.24 ($SiMe_3$), 19.72 ($SiCMe_3$), 27.26 [$SiC(CH_3)_3$]; ^{14}N-NMR ($CDCl_3$, CH_3NO_2 ext.): $\delta = -329$; ^{29}Si-NMR (CH_2Cl_2/C_6D_6, TMS int.): $\delta = 7.25$ ($SiMe_2CMe_3$), 12.88 ($SiMe_3$).

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P_4-Degradation with and without Disproportionation**

By *Alfred Schmidpeter**, *Günther Burget*, *Hans Georg von Schnering*, and *Dieter Weber*

White phosphorus is degraded nucleophilically by aqueous solutions of alkali metal hydroxides, e.g. according to the following equation

$$P_4 + 3\,OH^{\ominus} + H_2O \longrightarrow 3\,H_2PO_2^{\ominus} + PH_3$$

and thereby formally disproportionates into the P_4-fragments $3\,P^{\oplus}$ and $P^{3\ominus}$, which are however strongly modified by taking up $OH^{\ominus}$ and $H^{\oplus}$, respectively. Instead of using the hydroxide ion, we have now studied P_4-degradation with soft anionic bases $X^{\ominus}$ and obtained products in which the P_4-fragments are more easily recognized. The 4-valence electron particle $P^{\oplus}$ is stabilized by addition of the two ligands $X^{\ominus}$ to give the anion $PX_2^{\ominus}$ with an octet configuration at P, and the charge on $P^{3\ominus}$ is shared with a larger or smaller number of phosphorus atoms to form a polyphosphide [eq. (1)].

$$(n+1)/4\;\; P_4 + 2\,X^{\ominus} \longrightarrow PX_2^{\ominus} + P_n^{\ominus} \qquad (1)$$

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With X = CN, on a preparative scale, this reaction yields salts of the dicyanophosphide ion[2], which has previously been obtained by reduction of $P(CN)_3$[1]. Lithium triphenylstannide, alkali-metal alkyl- and arylphosphides[3], as well as alkali-metal phosphites, phosphonites, and phosphinites react analogously[4].

Moreover, in certain favorable cases P_4 may be degraded without disproportionation [eq. (2)]. Here, the base $X^{\ominus}$ effects breakdown of P_4 into two P_2-halves. Their 10-valence electron system (which in contrast to N_2 cannot sufficiently π-stabilize) is supplemented in this way with four electrons by addition of two $X^{\ominus}$ ligands.

$$1/2\,P_4 + 2\,X^{\ominus} \longrightarrow P_2X_2^{2\ominus} \qquad (2)$$

With NaX = sodium diethyl- and sodium diphenylphosphinite, both reactions were verified. Decisive is the molar ratio of P_4 to $X^{\ominus}$: If the molar ratio is 1 : 4 in tetrahydrofuran, the salt **1** forms momentarily and completely at room temperature [eq. (3) ≙ (2), X = PR_2O]. Excess base remains unreacted. Reduction of the amount of base to a level such that two phosphinite ligands are no longer available per P_2 moiety leads to disproportionation of a fraction of the phosphorus into **2a** and Na_3P_7 [(eq. (4) ≙ (1), X = PR_2O, n = 7/3]. At the molar ratio 1 : 2.4, only disproportionation occurs. Addition of still less base gives [e.g., according to eq. (5) ≙ (1), n = 8] as reduction products higher sodium polyphosphides which finally precipitate.

$$P_4 + 4\,NaOPR_2 \longrightarrow 2\,Na_2 \left[\begin{array}{l} R\quad\;\; R \\ O{=}P{-}P{-}P{=}O \\ R\quad\;\; R \\ \updownarrow \\ R\quad\;\; R \\ O{-}P{=}P{-}P{-}O \\ R\quad\;\; R \end{array}\right] \qquad (3)$$

1 : 4

1

$$5\,P_4 + 12\,MOPR_2 \longrightarrow 6\,M \left[\begin{array}{l} R\quad\;\; R \\ O{=}P{-}P{-}P{=}O \\ R\quad\;\; R \\ \updownarrow \\ R\quad\;\; R \\ O{=}P{-}P{=}P{-}O \\ R\quad\;\; R \end{array}\right] + 2\,M_3P_7 \qquad (4)$$

1 : 2.4

2

$$9\,P_4 + 8\,MOPR_2 \longrightarrow 4\,\mathbf{2} + 2\,M_2P_{16} \qquad (5)$$

1 : 0.9

a, M = Na; **b**, M = Li; R = Et, Ph

1a and **2a** differ markedly in their hydrolytic sensitivity: whereas **1a** is decomposed instantaneously by water, **2a** remains stable for several days.

In contrast to sodium phosphinites, lithium phosphinites react, even when present in a large excess, only in the molar ratio 1 : 2.4 according to eq. (4) with disproportionation to afford **2b** and Li_3P_7. The latter compound (just as Na_3P_7) can be identified by comparison of the ^{31}P-NMR spectra with those of authentic material[3b,5]. If the molar ratio P_4 : base is reduced to 1 : 0.9, in addition to **2b** an insoluble polyphosphide is formed; its composition, based on the stoichiometry of eq. (5), is Li_2P_{16}[3c]. Upon use of

even less lithium phosphinite, a part of the white phosphorus remains unreacted.

The structures of the compounds **2** and **1** are established by their characteristic ^{31}P-NMR signals (A_2X and $[AX]_2$ system, resp.) (Table 1); in addition, the structure of

Table 1. ^{31}P-NMR data for compounds **1** and **2** (in THF at room temperature) [a].

1 **2**

	M	R	δ^{31}P P2	δ^{31}P P1	^1J(P2–P1) [Hz]	^1J(P1–P3) [Hz]	^2J(P2–P3) [Hz]
1	Na	Et	82.2	−204.5	537.8	275.8	−4.3
	Na	Ph	69.4	−183.1	573.5	268.1	−3.4
2a	Na	Et	77.3	−154.3	395.0		
	Na	Ph	55.6	−116.4	397.7		
2b	Li	Et	79.1	−166.0	402.0		
	Li	Ph	58.8	−127.9	402.5		

[a] At lower temperatures, two isomers of the anion with almost identical ^{31}P-NMR data are observed for each of the compounds **1**.

2b (R = Ph) is confirmed by an X-ray structure analysis[6] (Fig. 1). In **2b** (R = Ph), lithium is not (as, for example, in $LiP(tBu)_2$[7] coordinated to phosphorus, but to the two oxygen atoms of the anion, underscoring the larger contribution of the mesomeric structure with the anionic charge at oxygen. The chelate six-membered ring has a boat conformation (with P1 and lithium out of the P_2O_2 plane). The PPP angle of 95.3(1)° corresponds, in particular, to that in

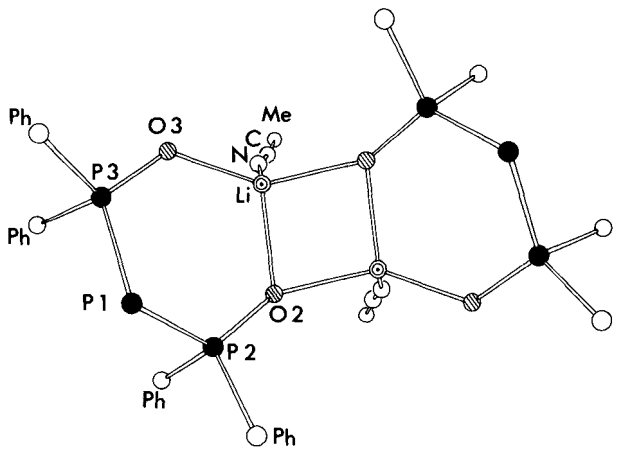

Fig. 1. Structure of $[[Ph_2(O)P-P-P(O)Ph_2]^{\ominus}Li^{\oplus}\cdot CH_3CN]_2$. **2b**, R = Ph, in the crystal. Only C1 of the phenyl groups are shown. Monoclinic, C2 (no. 5), $a = 2130.0(7)$, $b = 896.9(4)$, $c = 1522.2(14)$ pm, $\beta = 118.22(6)°$, $Z = 2$, $V = 2562.35 \times 10^6$ pm^3, structure solved by direct methods (SHELXTL 3.0), $R = 0.091$ ($R_w = 0.089$). Selected distances [pm] and angles [°]: P1-P2 212.3(5), P1-P3 215.9(5), P2-O2 150.5(7), P3-O3 150.3(7), O2-Li 198.9(25), O3-Li 185.0(27); P2-P1-P3 95.3(1), P1-P2-O2 118.2(4), P1-P3-O3 117.6(4), P3-O3-Li 129.3(9), P2-O2-Li 125.4(9), O2-Li-O3 107.6(10). Further details of the crystal structure investigation can be obtained from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, by quoting the depository number CSD 50917, the names of the authors, and the journal citation.

the pyrrolidinium salt **2**; M = $C_4H_{10}N$, R = *i*PrO[8]. Because of the distortion of the mirror symmetry of the ring, which arises from the dimerization, the two PP bonds are unequal in length and with 214.1 pm on average are somewhat longer than in the pyrrolidinium salt.

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[6] A solution of $LiPPh_2O$ (100 mmol) in 150 mL THF and P_4 (13.0 g, 105 mmol) is refluxed for 24 h. The black, somewhat caked solid precipitate is filtered off. The red filtrate is concentrated, and the colorless **2b**·CH_3CN (R = Ph) crystallized from it by addition of acetonitrile and pentane; yield 17.3 g (72%).
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[Li(tmeda)]$_3P_7$—A Solvated Ion Complex of Trilithium Heptaphosphide**

By *Wolfgang Hönle, Hans Georg von Schnering**, *Alfred Schmidpeter*, and *Günther Burget*

Crystalline solvates of salt-like compounds are intermediates of the transition from the polymeric structure formed by cations and anions to the solution in which solvated and separated ions predominate. The interchange from the structure with highly coordinated M^+ and X^- ions to the solvated ion complex or molecule involves a drastic reorganization. This is neatly exemplified in the case of the lithium phosphide Li_3P_7. The brilliant-yellow, *solvent-free* Li_3P_7[1] forms a highly coordinated structure without any indication of "Li_3P_7" units but with bonds from lithium to all phosphorus atoms. Crystalline Li_3P_7 does not dissolve in toluene, but does so very slowly in ethers, and only slowly so in ethylenediamine to give *colorless* solutions[2]. Solvated Li_3P_7 is also obtained as the *colorless solvate* $Li_3P_7(solv)_3$, however, in reactions in ethers[3–5]. In solution a valence fluctuation is observed in the P_7^{3-} ion[3–5]. The ^{31}P-NMR signals indicate ^{7}Li couplings[3]; hence, solvated Li_3P_7 ionic complexes are also present in solution, but no isolated P_7^{3-} ions, which is significant for the course of the valence fluctuation[6]. Consequently, the determination of the structure of a solvate seemed of utmost importance[7].

The first solvate isolated in crystalline form was [Li(tmeda)]$_3P_7$, formed on reaction of white phosphorus with $LiCH_2PPh_2$(tmeda) (tmeda = tetramethylethylenediamine)[8]. Alkali metal salts of Ph_2PX^- (X = O, NPh) effect a

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disproportionation of P_4 in $(XPPh_2)_2P^-$ with P^I as oxidized step and a polyphosphide as reduced step[9]. In the present case ($X=CH_2$) the oxidation product separated as a red oil and could not be identified, while the reduction product $[Li(tmeda)]_3P_7$ remained in solution and could be crystallized. Its ^{31}P-NMR spectrum shows a broad signal ($\delta=-122$, upfield) at room temperature, as in other $Li_3P_7(solv)_3$ solvates (solv = tetrahydrofuran, monoglyme)[3,4]. When solv = ethylenediamine, on the other hand, a sharp singlet with the same chemical shift is observed. This indicates that the fluctuation frequency depends not only on the cation but also on the coordinating solvent.

$[Li(tmeda)]_3P_7$ crystals already effloresce at room temperature, with loss of tmeda (analysis), and do not melt. The loss of tmeda can be monitored mass spectroscopically; it increases steadily with temperature up to 100 °C and, thereafter, very rapidly. The mass spectrum (180 °C, 70 eV) shows signals of high intensity for the ions $tmeda^+$ and P_4^- and, in particular, for fragments related with a—presumably tetrahedral—species $LiP_3(tmeda)^+$. The X-ray structure analysis shows the presence of an isolated, solvated ionic complex $[Li^+(tmeda)]_3P_7^{3-}$ with approximate 3m (C_{3v}) symmetry. The Li atoms are each coordinated in a distorted tetrahedron to two twofold bonded P atoms and the two N atoms of one tmeda molecule (Fig. 1). A particularly important feature is the bridge function of the Li atoms at the heptaphosphane(3) moiety, which apparently is also typical for other cations[1,2] and whose significance in organolithium compounds has recently again been pointed out[10]. The threefold bonded P atoms do not participate in the coordination of the Li atoms, which is typical for solvent-free polyphosphides. The bond lengths (Fig. 1)

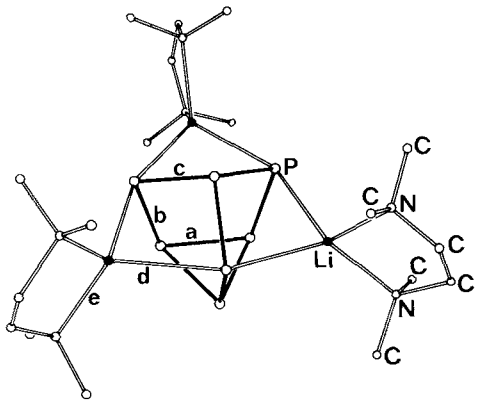

Fig. 1. Structure of the solvated ion complex $[Li(tmeda)]_3P_7$ in the crystal. Mean bond lengths: a = 225.5, b = 215.0, c = 220.4, d = 255.5, e = 207.1 pm.

show, with the sequence a > c > b and the relative height Q* of the polycycle, Q* = h/a = 302 pm/226 pm = 1.34 (h = distance between the apical P atom and the trigonal P_3 base), unequivocally the presence of an ionic P_7^{3-} framework[11]. The Li(tmeda) rings are twisted. The strong anisotropy of the thermal ellipsoids of the atoms in the Li(tmeda) rings can be ascribed to orientational disorder or, possibly also, to dynamic conformational changes.

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[8] The freshly prepared dark red solution of 20 mmol $LiCH_2PPh_2 \cdot tmeda$ [12] in tetrahydrofuran (20 mL) and *n*-hexane (20 mL) was treated with P_4 (2.48 g, 20 mmol) and the mixture heated under reflux for 30 min. A dark-red, oily precipitate was formed. The solution showed exclusively the ^{31}P-NMR signal of P_7^{3-}. Ca. 1.5 g of pale orange $Li_3P_7(tmeda)_3$ crystals separated out from the warm decanted red solution after 12 h at room temperature.

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Novel Double-Layered Annulenes—Models for the Investigation of Successive Electron Transfers**

By *Wolfgang Irmen, Walter Huber, Johann Lex,* and *Klaus Müllen**

The title compounds **1a**—**1c**, whose synthesis and structure elucidation will be described, form a novel type of double-layered molecules. In **1a**—**1c**, perimeter π-systems are linked by internal bridges, instead of by external side arms as, e.g., in phanes[1]. In principle, **1a**—**1c** can exist both in a *syn*(**A**) and an *anti*(**B**) conformation; the distance between layers can be controlled by the length of the alkanediyl bridge. The compounds **1a**—**1c** of this type, which are constructed from two separate electroactive groups, thus seem to be ideal models for successive electron transfers[2]. The characterization of the redox sequences from the monoanion up to the tetraanion show that the intramolecular through-space interaction between the electrophoric ring systems differs significantly for geometric reasons.

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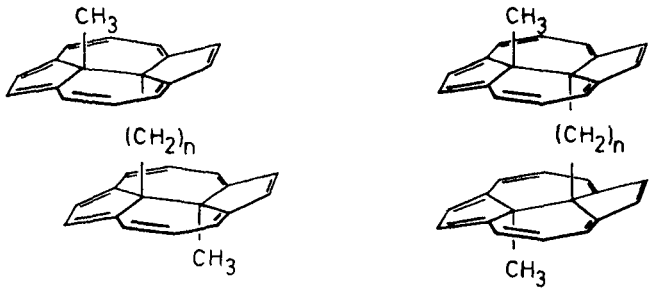
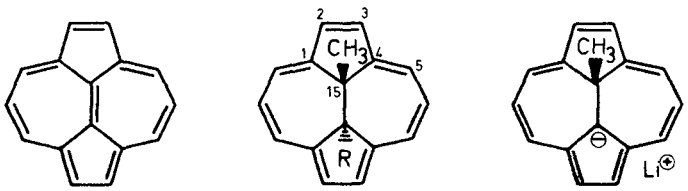


a, n = 3; **b**, n = 4; **c**, n = 8

On the basis of spectroscopic data[3], we reductively alkylated dicyclopenta[*ef*,*kl*]heptalene **2** and generated the bisadduct **3a**, a bridged [14]annulene, regioselectively via the dianion $2^{2\ominus}$[4]. The behavior of the monoanion **4**, which should be formed from $2^{2\ominus}/2\,Li^{\oplus}$ in the first step, remains an open question.



2 **3** **4**

3a, R = CH_3; **3b**, R = H; **3c**, R = OH;
3d—**f**, R = $(CH_2)_nCH_3$, n = 3, 5, 7;
3g—**j**, R = $(CH_2)_nBr$, n = 2, 3, 4, 8

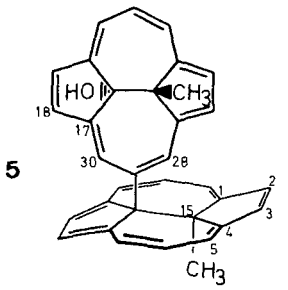
Table 1. ^{1}H-NMR chemical shifts (δ values; [D_8]THF, 300 MHz, −30°C) of the annulenes, **1a**—**1c**, **3b**, **3d** and **3f**, as well as those of the dianion $\mathbf{3d}^{2\ominus}$ and the tetraanion $\mathbf{1b}^{4\ominus}$; H-α to H-δ are the protons of the alkanediyl and alkyl chains. ESR coupling constants (a_H [mT], DME/HMPT, −80°C) of the radical anions $\mathbf{3a}^{\ominus\ominus}$, $\mathbf{1a}^{\ominus\ominus}$, and $\mathbf{1c}^{\ominus\ominus}$ (all ions as potassium salts).

	H-2,3,9,10	H-5,7,12,14	H-6,13	CH_3	H-α	H-β
1a	8.48/8.44	8.42/8.40	7.76	−4.94	−6.49	−5.11
1b	8.62/8.31	8.56/8.36	7.83	−4.83	−5.64	−3.66
1c[a]	8.73 — 8.68		8.01	−4.61	−4.89	−2.14
3b	8.99 — 8.73		8.06	−4.41	−4.77	
3d[b]	8.9 — 8.7		8.1	−4.5	−4.7	−1.8
3f[c]	8.81 — 8.74		8.08	−4.56	−4.69	−1.83
$\mathbf{3d}^{2\ominus}$[d]	0.15/0.16	0.20-0.26	−0.79	12.11	13.68	7.33
$\mathbf{1b}^{4\ominus}$**A**	0.82	0.50-0.83	−0.41	12.98	16.80	10.22
$\mathbf{1b}^{4\ominus}$**B**	0.45 — 0.27		−0.69	11.38	12.59	6.91
$\mathbf{3a}^{\ominus\ominus}$	0.157(4H)	0.085(4H)	0.482(2H)	0.021(6H)		
$\mathbf{1a}^{\ominus\ominus}$	0.078(8H)	0.046(8H)	0.241(4H)	<0.009		
$\mathbf{1c}^{\ominus\ominus}$	0.152(4H)	0.098(4H)	0.482(2H)	0.018(3H)		

[a] −0.98 (H-γ); −0.49 (H-δ). [b] 0.1 to −0.71 (H-γ, H-δ). [c] −0.51 (H-γ); 0.22 (H-δ). [d] 4.39 (H-γ); 2.38 (H-δ).

Reductive methylation of **2** with dimethylsulfate in liquid ammonia (Li, −78°C) affords the monomethyl derivative **3b** [m.p. 125°C, red needles; see Table 1]. **4** can be smoothly generated by deprotonation of **3b** [n-butyllithium, tetrahydrofuran (THF), 0°C]. The resonance of C-16 at $\delta = 103.0$ (sp^2-hybridized C-atom with strong charge-induced shielding) indicates the existence of the highest π-charge density in this position and explains the regioselective formation of **3a** in the second alkylation of **4**[5].

The system **4** has proven especially useful as central intermediate for further syntheses. Trapping of **4** with oxygen affords equal amounts of the alcohol **3c** and the coupling product **5**[6]. On reaction of **4** with 1-bromoalkanes or 1,n-dibromoalkanes, annulenes such as **3d**—**3f** or **3g**—**3j**, respectively, containing differently substituted bridges are formed. When a solution of **4** (THF, 0°C) is treated with an equal amount of **3h**—**3j** (THF) as alkylating agent under strict exclusion of air, the "double layers" of bridged annulenes **1a**—**1c** are formed in good yields (95, 86, and 95%, respectively). In the analogous reaction of **4** with the bromoethyl derivative **3g** the desired coupling product is not formed.



5

The electron absorption spectrum of **1c**[7]—with "decoupled" subunits—corresponds very closely to that of the model system **3a**; in **1a**, the extinctions are markedly smaller than in **3a**. The influence exerted by the superposed magnetic anisotropy of the two strongly diatropic annulene moieties in **1a**—**1c** on the bridge protons is verified by the resonance of these nuclei at extremely high field (see Table 1). Very informative here is a comparison with the chemical shifts of the "individual systems", e.g. **3d** and **3f**. Using the resonances of the bridge protons as probes, it was possible to measure experimentally the secondary magnetic fields due to ring currents.

Preliminary results of an X-ray structure analysis of **1b** show[8] that an *anti*-orientation of the annulene moieties with respect to the alkanediyl bridge (with all-*trans* conformation) is preferred in the crystal (cf. **B**).

The radical anions of **1a**—**1c** are generated by electrochemical reduction [dimethoxyethane (DME), $[N(C_4H_9)_4]ClO_4$] and by reduction with potassium in DME/hexamethylphosphoric acid triamide (HMPT) or in methyltetrahydrofuran (MTHF). They could be characterized by ESR and ENDOR spectroscopy; the radical anion of the [14]annulene **3a**[9] serves as reference system (see Table 1).

The magnitude and multiplicity of the ESR coupling constants derived from the primary spectrum of $\mathbf{1a}^{\ominus\ominus}$ prove that the spin density is delocalized over both annulene moieties. This bonding situation, however, necessitates a certain minimum separation of the π-systems: The radical anion $\mathbf{1c}^{\ominus\ominus}$ forms a structure with localization of the spin density within *one* π-fragment under all experimental conditions. The analogue $\mathbf{1b}^{\ominus\ominus}$ assumes a medium position, for its primary ESR spectrum can only be explained in terms of the concomitant existence of a spin-delocalized (70%) radical anion and a spin localized radical anion. Both in $\mathbf{1a}^{\ominus\ominus}$[10] as well as in $\mathbf{1b}^{\ominus\ominus}$ the relative proportion of the spin localized species can be increased by further reduction, i.e. by increasing the radical concentration. The same can be achieved with MTHF as solvent, which enhances the tendency to tight (contact) ion pairs, and thus impairs intramolecular electron transfer[2]. A transformation of the alternative radical anion struc-

tures[11] cannot be observed in the accessible temperature range (−90 to +20 °C).

Further reduction (K/DME/HMPT) of **1a**$^{\ominus\ominus}$ and **1b**$^{\ominus\ominus}$ brings about a decrease in the intensity of the ESR signals. The glassy, rigid solutions (−160 °C) give the typical (ESR-) splitting pattern of triplet radicals **1a**$^{2\ominus}$ and **1b**$^{2\ominus}$. From the zero field parameters [D = 6.75 mT (**1a**$^{2\ominus}$); 4.38 mT (**1b**$^{2\ominus}$)], the average separation of the electrons in the triplet can be estimated to be 7.4 and 8.6 Å, respectively[12]. These values would indicate an all-*trans* conformation of the alkanediyl chain, which guarantees the largest possible separation of the electrons in the individual π-fragments.

After longer reduction times, all compounds show the same ESR spectrum (in the case of **1a** and **1b** after the appearance of the triplet radical), which resembles the spectrum of a spin-localized monoanion, and is to be assigned to the respective radical trianion.

The end products of the reduction are, in all cases, the diamagnetic tetraanions (potassium salts), in whose ^{1}H-NMR spectroscopic description (see Table 1) that of the "monomeric" dianion **3d**$^{2\ominus}$ (2 K$^{\oplus}$) should be included:

- the conversion of the [14]annulene **3d** into a 16π-dianion generates a strongly paratropic compound, recognizable by the high-field resonance of the ring protons and the extreme down-field resonance of the bridge protons[13];
- the observation of corresponding signal positions, e.g., for **1b**$^{4\ominus}$ leads to the conclusion that the tetraanion is made up of two paratropic 16π-moieties. The down-field shift of the signal of the methylene protons H-α during the transition to the tetraanion is $\Delta\delta = 22.4$;
- according to the ^{1}H-NMR spectrum, the tetraanion **1b**$^{4\ominus}$ is present in two structural forms, **1b**$^{4\ominus}$**A** and **1b**$^{4\ominus}$**B** (6 : 5), which do not transform from one into the other even at room temperature. The ^{1}H-NMR chemical shifts of **1b**$^{4\ominus}$**B** are much more similar to those of **3d**$^{2\ominus}$ than those of **1b**$^{4\ominus}$**A** [shifts of the signals of the methyl protons: $\Delta\delta = 17.8$ (**1b**$^{4\ominus}$**A**), 16.2 (**1b**$^{4\ominus}$**B**), 16.5 (**3d**$^{2\ominus}$); center of gravity of the signals of the protons in the ion: $\delta = 0.51$ (**1b**$^{4\ominus}$**A**), 0.16 (**1b**$^{4\ominus}$**B**), −0.08 (**3d**$^{2\ominus}$)]. In **1b**$^{4\ominus}$**A**, both the bridge protons as well as the ring protons are additionally exposed to the deshielding effect of the "second" annulene system, whereas in **1b**$^{4\ominus}$**B** two "independent" perimeters appear to exist. It might therefore be assumed that the two ion-pair structures of the tetraanion differ in the conformation of the 1,4-disubstituted butane system.

Since the alkylation of the ionic intermediates **2**$^{2\ominus}$ and **4** is also suitable for the synthesis of oligomeric π-systems with more than two layers, redox studies on electroactive "polylayers" should be possible.

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[5] For preparative purposes, **4** can also be synthesized directly from **2**$^{2\ominus}$ by reaction with methyl bromide in the molar ratio 1 : 1, since the dianion reacts more rapidly with the electrophile than does the monoanion.
[6] The position of the annulene moiety in the shielding region of the second annulene is confirmed by the upfield resonance of the ring protons H-28, 30 at $\delta = 4.26$.
[7] **1a**: $\lambda_{max}(CH_2Cl_2) = 334$ ($\varepsilon = 189300$), 347 (sh) (102300), 398 (7010), 423 (9000), 447 (9800), 508 (152), 550 (280), 575 (287), 603 (636); **1c**: λ_{max} (CH_2Cl_2) = 315 (sh) ($\varepsilon = 55600$), 336 (241600), 348 (166700), 380 (7370), 397 (7250), 422 (10400), 446 (12100), 508 (145), 550 (290), 577 (553), 605 (732); **3a**: λ_{max} (C_6H_{12}) = 335 ($\varepsilon = 136300$); 346 (101900), 377 (3500), 397 (4020), 420 (5430), 440 (6200), 445 (6870), 507 (69), 550 (127), 575 (163), 603 (277).
[8] $a = 8.313(3)$, $b = 13.100(4)$, $c = 25.134(4)$ Å; Pbca, $Z = 4$. 1615 reflections ($I \geq 2\sigma(I)$), $R = 0.154$. The structure could not be refined further since the crystals of **1b** tend to undergo twinning. Nevertheless, it was possible to locate hydrogen atom positions from difference Fourier syntheses.
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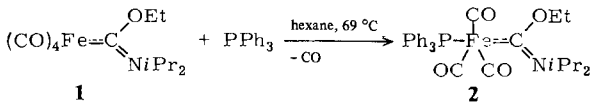
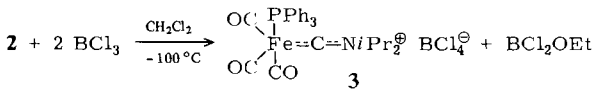
[(CO)$_3$PPh$_3$FeCN*i*Pr$_2$]$^{\oplus}$, a Novel Stable Carbyneiron-Complex Cation**

By *Ernst Otto Fischer**, *Johannes Schneider*, and *Dietmar Neugebauer*

Carbyne-transition metal complexes can be prepared from carbene complexes and halides of main group 3 elements[1]. If the iron is linked only to the carbene ligand and CO ligands in the educt this method fails. We therefore replaced the carbonyl group *trans* to the carbene ligand in the carbene complex tetracarbonyl[diisopropylamino(ethoxy)carbene]iron **1**[2] by a triphenylphosphane group and so obtained the stable compound **2**, which could be converted by reaction with boron trichloride into **3**. Tricarbonyl(diisopropylaminocarbyne)triphenylphosphaneiron tetrachloroborate **3** is a novel, isolable compound containing a complex cation with an iron-carbon triple bond[3]. A neutral *trans*-carbynehalogeno complex is not formed in this case, apparently because of the occupation of the *trans*-position by triphenylphosphane.



1 **2**



3

In the solid state, complexes **2** and **3** are briefly stable towards air at room temperature. **2** is only sparingly soluble in pentane, moderately soluble in diethyl ether, and readily soluble in dichloromethane; it crystallizes from pentane/dichloromethane (1 : 1) as a bright yellow powder. **3** is soluble only in polar solvents such as dichlorome-

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thane; it crystallizes in yellow-orange rhombs from diethyl ether/dichloromethane (1 : 1).

The spectroscopic data of **2** and **3** are listed in Table 1; Figure 1 shows the structure of the cation **3** (without coordinated dichloromethane).

Table 1. Spectroscopic data of **2** (top) and **3** (bottom).

IR (ν(CO), pentane): 1886 (m), 1878 (m) cm^{-1} [4, 5]

^{1}H-NMR ([D$_6$]acetone, rel. CD_3COCD_2H): $\delta = 7.43-7.72$ (15H, m; PPh_3), 6.19, 3.87 (each 1H, sept; $NCH(CH_3)_2$, *E/Z* isomerism), 4.79 (2H, q; OCH_2CH_3), 1.21–1.64 (15H, m; OCH_2CH_3, $NCH(CH_3)_2$, *E/Z* isomerism)

^{13}C-NMR (CD_2Cl_2, −20°C, rel. CD_2Cl_2): $\delta = 241.37$ (C(carbene), $^2J(CP) = 14.64$ Hz), 217.49 (C(CO), $^2J(CP) = 29.30$ Hz), 138.39, 135.47, 133.52, 132.87, 129.79, 128.49, 127.84 (C(PPh_3), 71.80 (OCH_2CH_3), 57.18, 50.03 ($NCH(CH_3)_2$, *E/Z* isomerism), 21.93, 19.65 ($NCH(CH_3)_2$, *E/Z* isomerism), 15.27 (OCH_2CH_3)

^{31}P-NMR ([D$_6$]acetone, rel. H_3PO_4): $\delta = 85.8$

MS (EI source): *m/z* 559 ($M^{\oplus}$), 531 ($M^{\oplus} - CO$), 475 ($M^{\oplus} - 3CO$)

IR (ν(CO), CH_2Cl_2): 2081 (vs), 2031 (s), 2009 (vs) cm^{-1} [4]

^{13}C-NMR (CD_2Cl_2, −20°C, rel. CD_2Cl_2): $\delta = 264.65$ (C10, $^2J(CP) = 43.95$ Hz), 203.78 C1,2,3, $^2J(CP) = 24.41$ Hz), 133.14, 132.49, 132.16, 129.56, 128.74 (C11,21,31), 22.14, 21.16 (C41,42,51,52, conformational isomerism). Signals of C4,5 presumably under the solvent signal

^{31}P-NMR (CD_2Cl_2, rel. H_3PO_4): $\delta = 57.3$

MS (FD source): *m/z* 514 ($M^{\oplus} - BCl_4$)

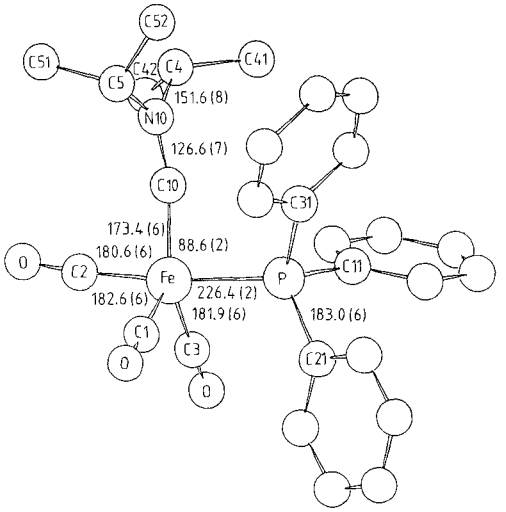

Fig. 1. Structure of the cation of **3** in the crystal (coordinated dichloromethane omitted) with important bond lengths [pm] and one angle [°].

The X-ray structure analysis[6] shows that the iron in **3** is coordinated in a distorted trigonal-bipyramid with the triphenylphosphane ligand and one carbonyl ligand in the apical positions. That is, the carbyne ligand is not in the *trans*-position to the triphenylphosphane group. The iron-carbyne carbon bond length (173.4(6) pm) is the shortest iron-carbon bond length so far observed, and is 28 pm shorter than the comparable iron-carbene carbon bond length in **1**[2]. The carbyne group is inclined towards the phosphane ligand, while the equatorial carbonyl groups are inclined away from it. The Fe–P bond length is 226.4(2) pm (for comparison, in carbynechromium complexes Cr–P 246.4 pm[7]); the Fe–C (carbonyl) bond length in the case of the axial CO groups (180.6(6) pm) is shorter than in the case of the equatorial groups (Fe–C1 182.6(6), Fe–C3 181.9(6) pm).

Experimental:

All operations were carried out under N_2 with anhydrous, oxygen-free solvents. **2**: A solution of **1** (8 g, 24.6 mmol) [2] in *n*-hexane (500 mL) was treated with 5.15 g (19.6 mmol) triphenylphosphane and the mixture heated under reflux for 5 h. On completion of reaction, **2** precipitated. The solvent was removed in a vacuum and the residue chromatographed on silica gel. After separation from unreacted carbene complex with pentane, **2** could be eluted with CH_2Cl_2. After removal of solvent, **2** was recrystallized from pentane/CH_2Cl_2; yield 8.11 g (59%), yellow crystals, m.p. 110–115°C (decomp.).—**3**: A solution of **2** (4.88 g, 8.7 mmol) in CH_2Cl_2 (100 mL) was treated at −100°C with 2 mL (23.0 mmol) BCl_3. The originally dark green solution was then allowed to warm within 3 h to −25°C, evaporated to 30 mL, and subsequently treated with precooled diethyl ether. **3** precipitated as yellow flocs. Analytically pure **3** was obtained as yellow-orange rhombs by repeated recrystallization from Et_2O/CH_2Cl_2 (1 : 1); yield 1.63 g (28%), m.p. 110–118°C (decomp.).

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CAS Registry numbers:
1, 91071-01-1; **2**, 92315-10-1; **3**·CH_2Cl_2, 92315-13-4; **3**, 92315-12-3; Fe, 7439-89-6; carbon, 7440-44-0

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[6] **2**: $a = 1312.0(2)$, $b = 1799.7(3)$, $c = 1468.3(3)$ pm, $\beta = 92.98(1)°$, $V = 3462.3 \times 10^6$ pm^3, $P2_1/n$, $Z = 4$, $\rho_{calc} = 1.44$ g/cm^3, $T = -40°C$, 4187 structural factors ($F \geq 3\sigma(F)$, $2° \leq 2\theta \leq 48°$), $Mo_{K\alpha}$ ($\lambda = 71.069$ pm, graphite monochromator), $R_1 = 0.063$, $R_2 = 0.072$ (Syntex/XTL); $BCl_4^{\ominus}$ and CH_2Cl_2 disordered. Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD 50961, the names of the authors, and the journal citation.
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Macrobicyclic Polyethers as V-Shaped Hosts for *cis*-Diammine-Transition Metal Complexes**

By *David R. Alston, Alexandra M. Z. Slawin, J. Fraser Stoddart**, and *David J. Williams*

In the supramolecular structures of the 1 : 1 adducts formed[1] between dibenzo-crown ethers of the general type DB3nCn (n = 8–10) and diammine-transition metal complexes such as $[Pt(bipy)(NH_3)_2][PF_6]_2$ {bipy = 2,2′-bipyridyl} and $[RhL(NH_3)_2][PF_6]$ {L = 1,5-cyclooctadiene (cod) or norbornadiene (nbd)}, X-ray analyses have shown that, without exception, the two NH_3 ligands straddle *one* of the polyether chains. This arrangement fails to make full use of the H bonding potential of these ligands. We have, therefore, designed host molecules (**1**) incorporating a *third* polyether chain between the *two* benzene rings. This constitutional modification produces *two* 20- or 23-membered

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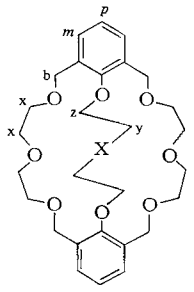
crown ether rings oriented side-by-side in an appropriate manner to facilitate H bonding with *both* of the NH_3 ligands.



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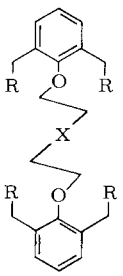

2, R = H
3, R = Br

a, X = O; **b**, X = OCH_2CH_2O; **c**, X = O–*o*-C_6H_4O; **d**, X = $OCMe_2CMe_2O$

Hosts[2] **1a**—**1d** which fulfill this constitutional criterion, have been synthesized from 2,6-dimethylphenol[3]. ^{1}H-NMR Chemical shift data reveal (Table 1) **1a**—**1d** form stable 1:1 adducts with $[Rh(cod)(NH_3)_2][PF_6]$ in CD_2Cl_2 solutions. Upfield shifts of the guest protons are accompanied by downfield shifts for the protons in the bridging aromatic rings of the hosts. Both **1a** and **1b** are conformationally mobile[4] on the ^{1}H-NMR time scale at room temperature as a result of rapid passage of the central polyether chain (seven atoms in **1a** and ten atoms in **1b**) through the middle of the (24-membered) macroring. This inversion process can be slowed down, as evidenced by the AB system ($\Delta\nu_{AB}=127$ Hz, $J_{AB}=10$ Hz) observed[4] for the benzylic-methylene protons in **1b** below the coalescence temperature ($T_c=-50$°C) and the line broadening observed[4] for the same protons in **1a** below −85°C (T_c=*ca.* −105°C). The rate constant (k_c) of 287 s^{-1} obtained[4] at the coalescence temperatures afforded $\Delta G_c^{\neq}$ values of *ca.* 7.8 and 10.4 kcal mol^{-1} for **1a** and **1b**, respectively. In the presence of 1 mol equiv of $[Rh(cod)(NH_3)_2][PF_6]$, the coalescence temperatures of the AB systems for the same probe protons in **1a** ($\Delta\nu_{AB}=85$ Hz, $J_{AB}=9.8$ Hz, $T_c=-48$°C) and **1b** ($\Delta\nu_{AB}=100$ Hz, $J_{AB}=9$ Hz, $T_c=12$°C) are much higher, corresponding to $k_c=196$ s^{-1} ($\Delta G_c^{\neq}=10.7$ kcal mol^{-1}) and to $k_c=228$ s^{-1} ($\Delta G_c^{\neq}=13.6$ kcal mol^{-1}), respectively. The $\Delta\Delta G_c^{\neq}$ values of *ca.* 2.9 and 3.2 kcal mol^{-1} for **1a** and **1b**, respectively, in the presence and absence of $[Rh(cod)(NH_3)_2][PF_6]$, indicate that these hosts form 1:1 adducts of comparable stabilities. This suggests that the macroring and phenolic oxygen atoms in the host are major sources of binding in these adducts, *i.e.* the constitution of the middle portion of the central polyether chain is relatively unimportant in this respect. This view is supported by (i) chemical shift data (Table 1) obtained on adduct formation by the more conformationally rigid[4] hosts **1c** and **1d**—the shifts compare favorably with those observed for **1a** and **1b**— and (ii) X-ray analyses[5] of the adducts with **1b** and **1c** (Fig. 1 and 2, resp.), which confirm the elegant structural suitability of these large bicyclic systems with 24-membered macrorings for optimum H bonding with *cis*-NH_3 ligands. Moreover, there is an obvious redundancy in the middle *two* oxygen atoms of the central polyether chains in *both* hosts. With one exception, namely N1···O40 in the **1c**-adduct (where N···O is 3.43 Å), the distances of the nitrogen atoms to the middle *two* oxygen atoms are all greater than 3.6 Å. The polyether components of the macrorings in the *two* hosts adopt very similar conformations (i.e. *a ag*$^-$*a ag*$^+$*a a*) from C1 to C9 and from C15 to C23, ensuring the encirclement of *both* *cis*-NH_3 ligands in the guest (cf. Fig. 1 and 2). Although alternating *gauche* helicities (i.e. *ag*$^-$*a ag*$^+$*a ag*$^-$*a* from C30 to C39) also characterize the C–C bonds in the central polyether chain of the **1b**-adduct, the enforced *syn*-rela-

Table 1. Selected ^{1}H-NMR data [a] for the 1:1 adducts of $[Rh(cod)(NH_3)_2][PF_6]$ and **1a**—**1d** in CD_2Cl_2 (δ values, TMS as int. standard).

Resonance	18C6	1a	1b	1c	1d
NH_3 [b]	2.39	2.00 (−0.39)	2.22 (−0.17)	2.22 (−0.17)	2.20 (−0.19)
(cod)-H^e [b]	2.39	2.00 (−0.39)	1.32 (−1.07)	1.52 (−0.87)	1.48 (−0.91)
(cod)-H^a [b]	1.85	1.59 (−0.26)	1.13 (−0.72)	1.27 (−0.58)	1.24 (−0.61)
(cod)-H^o [b]	4.07	3.54 (−0.53)	3.60 (−0.47)	— [d] — [d]	— [d] — [d]
p-Aryl-H [c]	—	7.18 (+0.17)	7.27 (+0.27)	7.20 (+0.15)	7.28 (+0.26)
m-Aryl-H [c]	—	7.39) (+0.14)	7.50 (+0.25)	7.51 (+0.23)	7.50 (+0.22)

[a] The spectra were recorded at room temperature on a 220-MHz spectrometer (Perkin Elmer R34). [b] The values in brackets indicate the extent to which signals of the guest protons (H^e=equatorial methylene proton; H^a=axial methylene proton; H^o=olefinic proton) are shifted relative to the corresponding signals in $[Rh(cod)(NH_3)_2\cdot 18C6][PF_6]$. [c] The values in brackets indicate the extent to which the signals of the bridging aromatic ring protons are shifted relative to the corresponding signals in the free hosts. [d] Signal obscured by signals for OCH_2 protons.

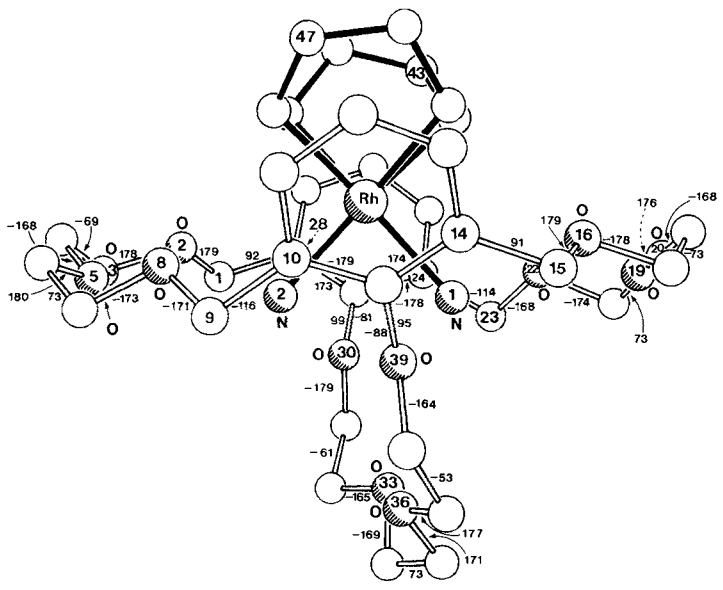

Fig. 1. Structure of $[Rh(cod)(NH_3)_2\cdot$ **1b**$][PF_6][CH_2Cl_2]$ in the crystal. Crystal data: monoclinic, $a=17.406(2)$, $b=14.768(2)$, $c=19.407(2)$ Å, $\beta=102.82(1)$°, $V=4865$ Å^3, space group, $P2_1/c$, $Z=4$, $\rho_c=1.42$ g cm^{-3}, μCu-$K_\alpha=49$ cm^{-1}, 4123 independent reflections with [$|F_o|>3\sigma(|F_o|)$, $\theta\leq 50$°], $R=0.063$, $R_w=0.069$. Torsional angles [°] associated with the polyether chains are shown beside the relevant bonds. *Both* NH_3 ligands have *two* distinct orientations. Distances for N1 to O16, O19, O22, and O39: 3.19, 3.05, 3.17, and 3.04 Å, respectively. Those for N2 to O2, O5, O8, and O30: 3.17, 3.07, 3.20, and 3.01 Å, respectively. Atoms N1 and N2 are inserted 0.56 and 0.53 Å, respectively, below the mean plane of the six peripheral oxygen atoms. Cleft angle between the mean planes of the aromatic rings is 63°. Separations between these mean planes and the nearest cod hydrogen atoms: [C10/14···H°(47)] 3.20, [C24/28···H$_c$(43)] 2.98 Å.

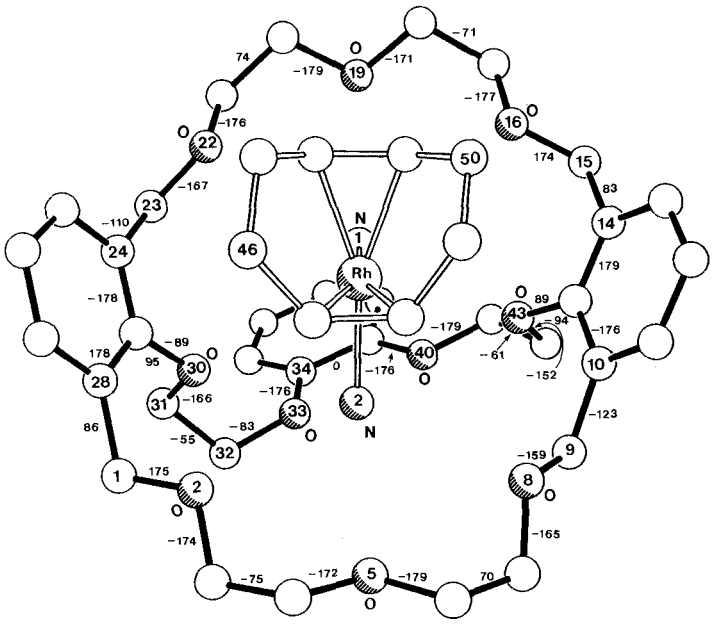

Fig. 2. Structure of $[Rh(cod)(NH_3)_2 \cdot \mathbf{1c}][PF_6][CH_2Cl_2]$ in the crystal. Crystal data: triclinic $a = 12.984(2)$, $b = 13.674(4)$, $c = 13.973(2)$ Å, $\alpha = 89.02(2)$, $\beta = 84.13(1)$, $\gamma = 86.05(2)°$, $V = 2462$ Å, space group $P\bar{1}$, $Z = 2$, $\rho_c = 1.47$ g cm^{-3}, 4400 independent reflections with $[|F_0| > 3\sigma(|F_0|)$, $\theta \leq 50°]$, $R = 0.042$, $R_w = 0.046$. Torsional angles [°] associated with the polyether chains are shown beside the relevant bonds. *One* NH_3 ligand has *two* distinct orientations. Distances for N1 to O16, O19, O22, and O43: 3.26, 3.04, 3.05, and 3.00 Å, respectively. Those for N2 to O2, O5, O8, and O30: 3.13, 3.08, 3.12, and 3.07 Å, respectively. Atoms N1 and N2 are inserted 0.62 and 0.63 Å, respectively, below the mean plane of the six peripheral oxygen atoms. Cleft angle between the mean planes of the aromatic rings is 68°. Separation between these planes and the nearest cod hydrogen atoms: [C10/14···H^c(50)] 3.13; [C24/28···H^c(46)] 3.24.

tionship of the catechol oxygen atoms, O33 and O40, in the **1c**-adduct is accommodated by a substantial distortion of the C31–C32–O33–C34 torsional angle.

The X-ray structure analysis[5] of free **1b** (Fig. 3) reveals the extent to which the polyether chains have to reorganize themselves conformationally in order to bind the guest.

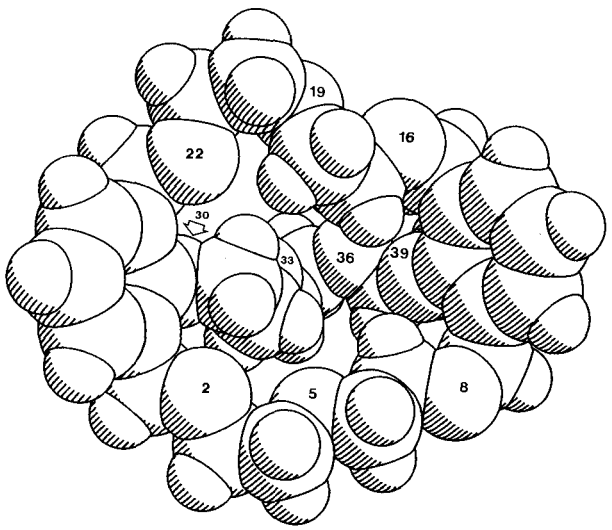

Fig. 3. Space-filling representation of the structure of **1b** with the oxygen atoms numbered. Crystal data: orthorhombic, $a = 12.997(3)$, $b = 14.139(2)$, $c = 16.072(2)$ Å, $V = 2953$ Å^3, space group $P2_12_12_1$, $Z = 4$, $\rho_c = 1.27$ g cm^{-3}, 2068 independent reflections with $[|F_0| > 3\sigma(|F_0|)$, $\theta \leq 58°]$, $R = 0.046$, $R_w = 0.049$. Cleft angle between the mean planes of the aromatic rings is 76°.

With its V-shaped conformation, free **1b** has structural characteristics similar to those of bound **1b**. However, it is noticeable that *four* of the oxygen atoms (O8, O16, O19, and O30) are no longer directed into the cavity and instead *five* methylene groups (on C7, C17, C18, C31, and C32) are oriented inwards. Although these particular conformational changes reflect the inability of **1b** to sustain an organized cavity in the absence of a guest, the host and its analogues (**1a**, **1c**, **1d**) clearly offer a much improved molecular receptor design for transition metal *cis*-diammines over the simpler DB3nCn ethers[1].

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[2] Since the first report (F. Vögtle, E. Weber, *Angew. Chem. 86* (1974) 126; *Angew. Chem. Int. Ed. Engl. 13* (1974) 149) of the use of 2-substituted-1,3-xylylene units in macrocyclic hosts, they have found wide application: see, for example, M. Newcomh, S. S. Moore, D. J. Cram, *J. Am. Chem. Soc. 99* (1977) 6405; M. van der Leij, H. J. Oosternik, R. H. Hall, D. N. Reinhoudt, *Tetrahedron 37* (1981) 3661; M. A. McKervey, T. O'Connor, *J. Chem. Soc. Chem. Commun. 1982*, 655.

[3] A strategy similar to that adopted (W. D. Curtis, J. F. Stoddart, G. H. Jones, *J. Chem. Soc. Perkin Trans. I 1977*, 785) in the preparation of 1,6,13,18,25,30-hexaoxa[6.6.6](1,3,5)cyclophane from phloroglucinol was employed. Experimental: Reactions (NaH, THF) of 2,6-dimethylphenol with the bistosylates (J. Dale, P. O. Kristiansen, *Acta Chem. Scand. 26* (1972) 1471) of diethylene and triethylene glycols, and with the bistosylates (L. C. Hodgkinson, I. O. Sutherland, *J. Chem. Soc. Perkin Trans. I 1979*, 1908 and N. Ando, S. Ohi, Y. Yamamoto, J. Oda, Y. Inouye, *Bull. Inst. Chem. Res., Kyoto Univ. 58* (1980) 293, respectively) of the bis-2-hydroxyethyl ethers derived from catechol and pinacol, afforded the acyclic polyethers **2a** (88%, m.p. 28—30°C), **2b** (67%, m.p. 37—39°C), **2c** (18%, m.p. 102—103°C), and **2d** (68%, m.p. 77—77.5°C), respectively. Photochemical bromination (NBS, CCl_4) of **2a**—**2d** gave the corresponding tetrabromides **3a** (10%, m.p. 125—126°C), **3b** (28%, m.p. 116—117°C), **3c** (27%, m.p. 121—123°C), and **3d** (9%, m.p. 116—117°C). Reactions (NaH, THF, high dil.) of **3a**—**3d** with diethylene glycol in the molar ratio 1:2 afforded, **1a** [27%, oil, ^{1}H-NMR (CD_2Cl_2): $\delta = 3.55$—3.73 (16 H^x, m), 3.88 (4 H^y, t), 4.16 (4 H^z, t), 4.52 (8 H^b, s), 7.01 (2 H^p, t), 7.25 (4 H^m, t)]: **1b** [21%, m.p. 113—115°C, single crystals suitable for X-ray (cf. Fig. 3) from EtOAc-light petroleum, ^{1}H-NMR (CD_2Cl_2): $\delta = 3.56$ (16 H^x, bs), 3.77 (4 H, s, OCH_2CH_2O), 3.91 (4 H^y, t), 4.04 (4 H^z, t), 4.52 (8 H^b, s), 7.00 (2 H^p, t), 7.25 (4 H^m, d)]; **1c** [31%, m.p. 122—124°C, ^{1}H-NMR (CD_2Cl_2): $\delta = 3.55$ (16 H^x, bs), 4.25 and 4.85 (8 H^b, AB system), 4.25—4.42 (4 H^y + 4 H^z, m), 6.99—7.16 (2 H^p + C_6H_4, m), 7.28 (4 H^m, d)]; **1d** [45%, m.p. 123—124°C, ^{1}H-NMR (CD_2Cl_2): $\delta = 1.30$ (12 H, s, CH_3), 3.58 (16 H^x, bs), 3.96 (4 H^y + 4 H^z, s), 4.24 and 4.80 (8 H^b, AB system), 7.02 (2 H^p, t), 7.28 (4 H^m, d). The crystalline **1b**- and **1c**-adducts, m.p. 155—157°C and 136—139°C, respectively, were obtained by layering Et_2O on top of CH_2Cl_2 solutions (1:1 stoichiometries). All new compounds and crystalline adducts gave satisfactory elemental analyses and spectroscopic data.

[4] The benzylic methylene protons H^b of the hosts **1a** and **1b** appear as singlets in CD_2Cl_2 at room temperature, whereas those of the hosts **1c** and **1d** gave AB systems. In both cases, the AB systems showed no signs of coalescence to singlets when $Cl_2C{=}CCl_2$ solutions of **1c** and **1d** were heated up to +120°C. Values for k_c were calculated using the approximation

$$k_c = \pi[(\nu_A - \nu_B)^2 + 6J_{AB}^2]^{1/2}/(2)^{1/2}.$$

For **1a**, where $\Delta\nu_{AB}$ and J_{AB} were not accessible in CD_2Cl_2, these parameters and hence k_c were assumed to be similar to those obtained for **1b**. In fact the $\Delta G_c^{\ddagger}$ value quoted for **1a** remains almost unchanged over a ±25 Hz uncertainty range in $\Delta\nu_{AB}$.

[5] Data were measured on a Nicolet R3m diffractometer using the ω-scan routine with graphite-monochromated $Cu_{K\alpha}$ radiation. The data for the two adducts were corrected for absorption. The structures of these adducts were solved by the heavy atom method and that of the free crown **1b** by direct methods. All three structures were refined anisotropically. Further details of the crystal structure investigations can be obtained from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.

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Crown Ether Complexes of Phosphonium Salts—The X-Ray Structure Analysis of $[(Ph_3PMe)_2 \cdot [18]Crown\text{-}6][PF_6]_2$**

By *Billy L. Allwood, Howard M. Colquhoun, John Crosby, David A. Pears, J. Fraser Stoddart**, and *David J. Williams*

The acidity of α-CH groups in alkylphosphonium cations, which has long been recognized and which forms the basis of the phosphonium ylide chemistry of *Wittig*[1], suggested to us that such cations[2] might form discrete complexes with crown ethers through C–H···O hydrogen bonding. Moreover, it has been shown[3–6] that certain neutral molecules such as $MeNO_2$, MeCN, and Me_2SO_2, $NCCH_2CN$, which also contain polar C–H bonds, do indeed bind to [18]crown-6 (18C6) *via* C–H···O interactions.

Here, we report on the ability[7] of $[Ph_3PMe][PF_6]$ to form a crystalline complex with 18C6 and on the X-ray crystal structure (Fig. 1 and 2) of this complex[8] with its many interesting and unusual features. The two $[Ph_3PMe]^{\oplus}$ ions lie propeller-like on a common 3-fold axis with the axial symmetry coincident with the P–Me···Me′–P′ direction, and the 18C6 host with its all-*gauche* conformation is positioned about a 3-fold inversion center. As a whole, the 2:1 complex has very high crystallographic $\bar{3}$ (S_6) symmetry[9]. All methyl H atoms are involved in discrete H bonds to single O atoms. The C–H···O bond distances of 3.600 Å are exceptionally long (H···O distance = 2.67 Å). The most significant feature of the H bonding is that it is directed to the face of the crown furthest away from the bound substrate, i.e. each $[Ph_3PMe]^{\oplus}$ ion H bonds, respectively, to the *further* triangle of O atoms. Although this disposition of H bonding, involving the so-called[10] nesting arrangement, has been reported previously[11] for the 1:1 crystalline complex formed between $[H_2NNH_3][ClO_4]$ and 18C6, this is the first occasion, to our knowledge, where *both* guests in a 2:1 complex with 18C6 adopt nesting positions rather than so-called[10] perching arrangements[12]. An interesting minor, and not necessarily statistically significant feature of this unexpected H bonding pattern is the contraction of the Me group H–C–H angles. These are reduced[13] from normal tetrahedral values to 102°, thus allowing the H atoms to penetrate more deeply into the 18C6 host without bringing the C atoms of the Me and Me′ groups in the bound guests unacceptably close together (C(Me)···C(Me′) = 4.10 Å). A further repercussion of the nesting geometries of the twin guests is an unusual almost perpendicular approach of the C–O and H–O vectors to the associated COC planes ($\theta_C = 78°$; $\theta_H = 82°$); by the same token, the *nearer* triangles of oxygen atoms are oriented ($\theta_C = 6°$, $\theta_P = 14°$) towards the positively charged guest cations with C(Me,Me′)···O = 3.36 Å and P,P′···O = 4.6 Å, thus probably conferring some electrostatic stabilization upon the 2:1 complex.

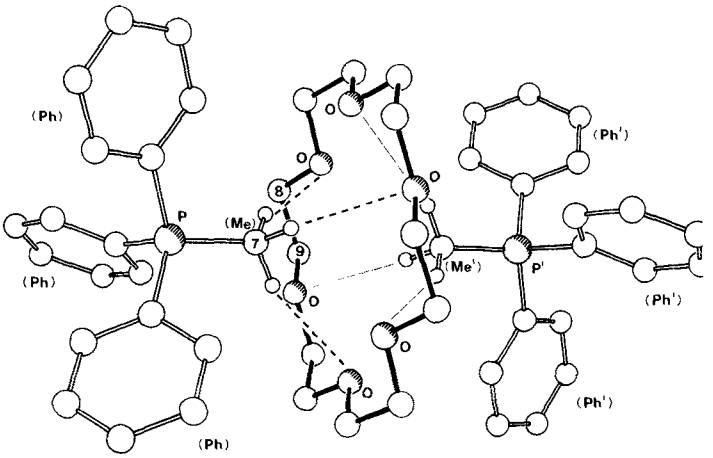

Fig. 1. Structure of $[(Ph_3PMe)_2 \cdot 18C6][PF_6]_2$ in the crystal. Bond lengths [Å] in host: C8-C9 1.495(5), C8-O 1.419(4), C(9)-O 1.413(4). Bond angles [°] in host: CCO 108.9(3), 109.7(3), COC 112.4(3). Torsional angles [°] in host: |CCOC| 179.6(3), 178.5(3), |OCCO| 66.2(5). Bond lengths [Å] in guest: P-C(Ph) 1.796(3), P-C(Me) 1.779(6), C(Me)-H 0.97(3). Bond angles [°] in guest: C(Me)-P-C(Ph) 109.8(1), P-C(Me)-H 116(3), H-C(Me)-H 102(3). C-H···O bond distance 3.600 Å. C-H···O bond angle 163°.—Distance [Å] of C(Me) to mean plane of the (a) near and (b) far triangles of O atoms 1.841 and 2.258, respectively.

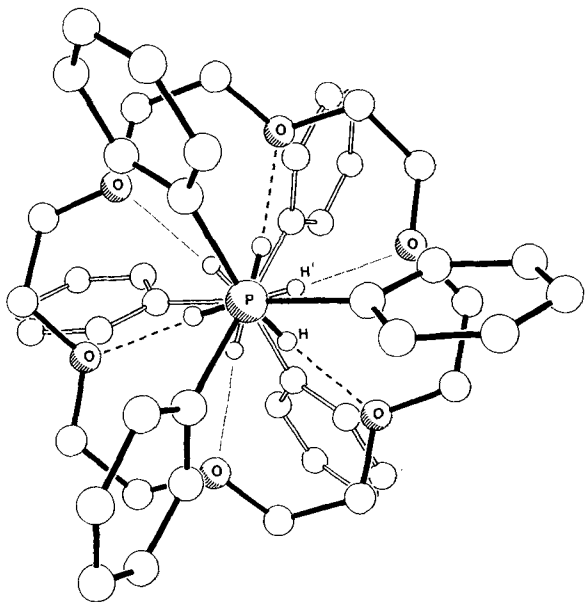

Fig. 2. View of $[(Ph_3PMe)_2 \cdot 18C6][PF_6]_2$ along the C_3 axis. The bonds in the distant guest cation are open.

The ^{1}H-NMR spectrum of $[Ph_3PMe][PF_6]$ in CD_2Cl_2 is identical (the Me doublet appears at $\delta = 2.77$) with that observed[7] for the 2:1 complex. Although this observation could be interpreted as evidence for marked dissociation of the complex in CD_2Cl_2 solution, it is revealing that, when the ^{1}H-NMR spectra of $[Ph_3PMe][PF_6]$, free and in the presence of 1 mol equiv of 18C6 are recorded in CD_2Cl_2–C_6D_6 (1:1), the methyl doublet resonates at $\delta = 2.45$ and 2.42, respectively. Moreover, addition of another molar equivalent of 18C6 causes the methyl doublet to move to even higher field ($\delta = 2.38$) indicating indeed

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that binding is weak. The upfield shift of the methyl signal on complexation is in marked contrast[14] to the downfield shifts characteristic of most H bonded systems. However, this shift may reflect slight changes induced in the relative orientations of the phenyl and methyl groups by the approach of the crown ether to the guest cation. Under such circumstances, intramolecular aromatic ring current effects will probably influence the observed chemical shift of the methyl group in the $[Ph_3PMe]^{\oplus}$ cation.

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CAS Registry number:
$[(PR_3PMe)_2 \cdot 18C6][PF_6]_2$, 92346-47-9

[1] *Top. Curr. Chem. 109* (1983).

[2] As far as alkylammonium cations are concerned, the strengths of complexes in MeOH decrease (R. M. Izatt, N. E. Izatt, B. E. Rossiter, J. J. Christensen, B. L. Haymore, *Science 199* (1978) 994) in the order $NH_4^{\oplus}$, $RNH_3^{\oplus} > R_2NH_2^{\oplus} > R_3NH^{\oplus}$ to the extent that macrocycles of the 18C6 type do not bind $R_4N^{\oplus}$ ions (B. Roland, J. Smid, *J. Am. Chem. Soc. 105* (1983) 5269). However, nitrogen ylides are not nearly as stable as their phosphorus counterparts, and encouragingly, certain features of the ^{1}H-NMR spectra of alkylphosphonium salts ($R_4P^{\oplus}X^{\ominus}$ where X = Cl, Br, I) have been interpreted (L. V. Nesterov, N. A. Aleksandrova, I. D. Temyachev, A. A. Musina, R. G. Gainullina, *Zh. Obshch. Khim. 47* (1977) 1259; *Chem. Abstr. 87* (1977) 117203f) in terms of C–H···X hydrogen bond formation.

[3] F. Vögtle, E. Weber in S. Patai: *The Chemistry of Functional Groups. Supplement E: The Chemistry of Ethers, Crown Ethers, Hydroxyl Groups, and their Sulphur Analogues*, Wiley, Chichester 1980, p. 59; F. Vögtle, H. Sieger, W. M. Müller, *Top. Curr. Chem. 98* (1981) 107.

[4] J. A. Bandy, M. R. Truter, F. Vögtle, *Acta Crystallogr. B37* (1981) 1568.

[5] J. A. A. de Boer, D. N. Reinhoudt, S. Harkema, G. J. Hummel, F. de Jong, *J. Am. Chem. Soc. 104* (1982) 4073.

[6] A. Elbasyouny, H. J. Brügge, K. von Deuten, M. Dickel, A. Knöchel, K. U. Koch, J. Kopf, D. Melzer, G. Rudolph, *J. Am. Chem. Soc. 105* (1983) 6568.

[7] Experimental: $[(Ph_3PMe)_2 \cdot 18C6][PF_6]_2$: $[Ph_3PMe][PF_6]$ (64 mg, 0.151 mmol) and 18C6 (20 mg, 0.075 mmol) were dissolved in the minimum volume of warm MeOH; long needle-shaped crystals, suitable for X-ray investigation, were obtained by vapor diffusion using light petroleum (P. G. Jones, *Chem. Brit. 17* (1981) 222). After 16 h, the crystals were filtered off, washed with Et_2O, and dried. Yield 62 mg (75%); m.p. 141–143 °C; ^{1}H-NMR (CD_2Cl_2): $\delta = 2.77$ (6H, d, $J_{PH} = 12$ Hz, Me), 3.59 (24H, s, OCH_2), 7.55–7.94 (30H, m, Ph).

[8] The complex is rhombohedral, $a = 11.592(3)$ Å, $\gamma = 71.39(2)°$, $U = 1357$ Å, space group $R\bar{3}$, $Z = 1$, $\rho_c = 1.36$ g cm^{-3}. Data were measured on a Nicolet R3m diffractometer with $Cu_{K\alpha}$ radiation (graphite monochromated) and using ω-scans. The structure was solved by the heavy atom method. The unique methyl hydrogen atom was clearly located in a ΔF map and refined isotropically; the remaining non-hydrogen atoms were refined anisotropically to give $R = 0.064$ ($R_w = 0.079$) for 1192 independent observed reflections [$\theta \leq 58°$, $|F_o| > 3\sigma(|F_o|)$]. Further details of the crystal structure investigation can be obtained from the Director of Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.

[9] The $PF_6^{\ominus}$ ion lies on a crystallographic 3-fold axis and is involved in only one short intermolecular contact (3.25 Å) between one of the F atoms and a phenyl ring C atom; the H···F distance is 2.65 Å.

[10] D. J. Cram, K. N. Trueblood, *Top. Curr. Chem. 98* (1981) 43.

[11] K. N. Trueblood, C. B. Knobler, D. S. Lawrence, R. V. Stevens, *J. Am. Chem. Soc. 104* (1982) 1355.

[12] The double perching arrangement has been observed in the X-ray crystal structures of a number of 2:1 complexes between CH-acidic neutral guests and 18C6: for example, Me_2SO_2 [4] and $MeNO_2$ [5].

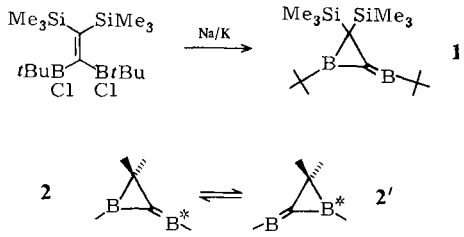
[13] Apart from exhibiting a P-C(Ph) bond length (1.795 Å) that is slightly longer than the P-C(Me) bond length (1.796 Å), the structure of the guest cation is very similar to those reported (see, for example, F. J. Hollander, D. H. Templeton, A. Zalkin, *Inorg. Chem. 12* (1973) 2262 and R. E. Cramer, D. M. Ho, W. van Doorne, J. A. Ibers, T. Norton, M. Kashiwagi, *ibid. 20* (1981) 2457) for the $[Ph_3PMe]^{\oplus}$ cation.

[14] Indeed, the Me doublet in [Ph$_3$PMe]Br resonates at $\delta = 3.18$ in CD_2Cl_2–C_6D_6 (1:1) indicating a strong C–H···Br hydrogen bonding interaction.

An Extraordinary Structure and Topomerization Mechanism for "Diboramethylenecyclopropane"**

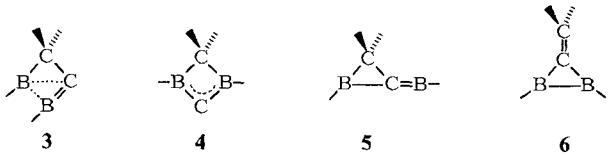
By *Peter H. M. Budzelaar, Paul von Ragué Schleyer**, and *Karsten Krogh-Jespersen**

Compounds containing a B–C double bond were unknown until the recent report by *Berndt* et al., claiming the synthesis of a diboramethylenecyclopropane, **1**[1]. The compound was found to undergo a rapid topomerization at room temperature (activation energy 11.4 kcal/mol), represented by the equilibrium **2** ⇌ **2′**.



Our further theoretical study of various $C_2B_2H_4$ isomers[2] now leads us to propose a related but significantly different structure (still containing a B=C bond) for **1**, and also to confirm a pathway for its topomerization suggested by *Berndt* et al.[3]. The $C_2B_2H_4$ species relevant to the present discussion are the isomers **2**–**6**. Geometries were optimized at the Hartree-Fock (HF) level using the split-valence plus polarization 6-31G* basis set, and energies were then obtained from single-point calculations at these optimized geometries using Møller-Plesset electron correlation estimates to third order (MP3)[4]. Table 1 gives the relative energies of **3**–**6**.

While the "classical" diboramethylene-cyclopropane structure **2** is indicated to be a local minimum with small



3 **4** **5** **6**

Table 1. Relative energies of **3**–**6** and substituent effects [a].

Compound	$E_{rel.}$ [b] $C_2B_2H_4$	Substituent Effects [c] CH_3 at B	SiH_3 at C	$E_{rel.}$ [d] $(H_3Si)_2CC(BCH_3)_2$
3	0	0	0	0
4	14.3	−5.6	1.4	10.2
5	26.2	−7.3	−3.6	15.3
6	24.4	1.9	−2.5	23.8

[a] Energies in kcal/mol, relative to **3** ≡ 0 kcal/mol. [b] MP3/6-31G*//6-31G*. [c] Single point HF/6-31G with HF/6-31G* optimized skeleton geometries and standard bond lengths and angles for the XH_3 substituents. [d] Values estimated by assuming additivity of substituent effects (see text).

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basis sets (e.g., 3-21G), this is *not* so at the HF/6-31G* level: optimization (starting with the 3-21G geometry for **2**) gives structure **3** directly. The carbene **4**[2d,3] (C_{2v} symmetry) corresponded to a local minimum at all theoretical levels employed. This means that a transition state (roughly resembling **2**) must separate **3** and **4**. This was located (**5**) at 6-31G*; some geometrical details are provided (Fig. 1). Finally, structure **6**, another possible species on the rearrangement pathway was considered (Table 1)[2]. Since **3** is by far the most stable of the $C_2B_2H_4$ isomers examined here, we suggest that *Berndt*'s "diboramethylenecyclopropane" **1**[1] may have a similar structure.—The spectroscopic data obtained for **1** may also be reconciled with a structure related to **3**.

The curious species **3** has normal B1–C1 and C1–C2 σ-bonds and a three-center π-bond (C2-B2-B1) (see Fig. 1). Only four electrons are involved in bonding the σ-framework of the B1C2B2 ring (Fig. 1). The bonding Walsh-type orbital σ_2 is occupied, but there is no antibonding counterpart to σ_2. This results in weak B1-C2 and B1-B2 bonds (represented here by dotted lines) and a strong C2-B2 double bond[5].

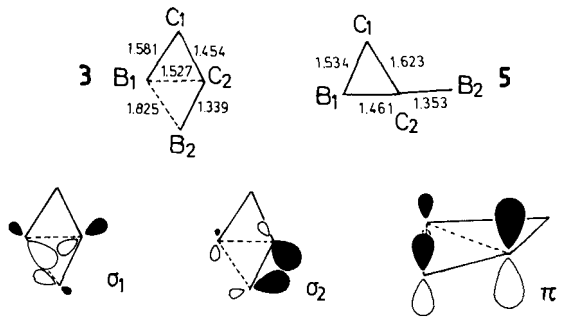

Fig. 1. Calculated bond lengths [Å] in **3** and **5** (top) and a schematic representation of the orbitals responsible for the bonding in the B1C2B2-ring of **3** (bottom).

What is the mechanism of the topomerization of **1** (modeled in our study by **3**)? The two obvious possibilities involving only planar species are:

$$\mathbf{4} \rightleftharpoons [\mathbf{5}] \rightleftharpoons \mathbf{3} \rightleftharpoons [\mathbf{6}]$$
(path 1) (path 1)

We have also searched for possible non-planar pathways, but have not found any likely candidates. Thus, the barrier for the topomerization of **3** is either 26.2 kcal/mol (path 1) or 23.7 kcal/mol (path 2). Before comparing this with the experimental value of 11.4 kcal/mol[1] for *Berndt*'s compound **1**, however, we have to take into account the electronic and steric effects of the substituents. The electronic effects have been estimated by modeling $SiMe_3$ and *t*Bu in **1** by SiH_3 and CH_3 groups, respectively. Relative to **3**, these groups lower the energy of **4** and **5**, but hardly affect that of **6** (Table 1, last column). Thus, the energy of path 1 is lowered while that of path 2 remains virtually unchanged. Hence, for the particular choice of substituents in **1**, path 2 can be ruled out, since it is ca. 10 kcal/mol higher in energy. Steric effects will be important for **3**, where the larger *t*Bu substituents on boron are forced close together. This should destabilize **3** by a few kcal/mol relative to **4** and **5**, and reduce the topomerization barrier further below the estimated value of 15.3 kcal/mol obtained by assuming additivity of the substituent effects. We conclude that path 1 can account for the observed topomerization barrier. The intermediacy of **4** in the proposed mechanism can also explain some of the observed reactions of **1**[3].

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[1] H. Klusik, A. Berndt, *Angew. Chem. 95* (1983) 895; *Angew. Chem. Int. Ed. Engl. 22* (1983) 877.

[2] a) K. Krogh-Jespersen, D. Cremer, D. Poppinger, J. A. Pople, P. von R. Schleyer, J. Chandrasekhar, *J. Am. Chem. Soc. 101* (1979) 4843; b) K. Krogh-Jespersen, D. Cremer, J. D. Dill, J. A. Pople, P. von R. Schleyer, *ibid. 103* (1981) 2589; c) P. von R. Schleyer, P. H. M. Budzelaar, D. Cremer, E. Kraka, *Angew. Chem. 96* (1984) 374; *Angew. Chem. Int. Ed. Engl. 23* (1984) 374; d) P. H. M. Budzelaar, P. von R. Schleyer, T. Clark, K. Krogh-Jespersen, unpublished.

[3] H. Klusik, Dissertation, Universität Marburg 1983; R. Wehrmann, H. Klusik, A. Berndt, *Angew. Chem. 96* (1984) 810; *Angew. Chem. Int. Ed. Engl. 23* (1984) 826.

[4] The GAUSSIAN 82 series of programs were employed (J. S. Binkley, M. Frisch, K. Raghavachari, D. J. DeFrees, H. B. Schlegel, R. A. Whiteside, E. Fluder, R. Seeger and J. A. Pople, GAUSSIAN 82, release A), with the standard basis sets and correlation treatments included in these programs.

[5] Recent calculations on **3** are in agreement with our calculations (G. Frenking, H. F. Schaeffer III, *Chem. Phys. Lett.*, in press.

1,3-Diboretanes**

By *Rolf Wehrmann, Hartmut Klusik,* and *Armin Berndt**

Dedicated to Professor Roland Köster on the occasion of his 60th birthday

1,3-Diboretane has so far merely been the subject of theoretical studies[1]. Herein we report the synthesis and characterization of the derivatives **3**—**5**.

The ethenylidene-1,3-diboretane **3** is formed as sole product on heating a mixture of 2-*tert*-butylborandiylborirane **1**[2,3] and bis(trimethylsilyl)acetylene in pentane under reflux for ten days. In this reaction, **1** behaves as if it is initially converted into the carbene **2**[4,5]. This behavior is also observed in the reaction of **1** with triphenylarsane and the well known carbene trapping reagent[6] triphenylphosphane, which leads at 20°C to the ylides **4a** and **4b**; the reaction with PPh_3 leads to formation of equal amounts of **4b** and the 1,3-dihydro-1,3-diborete **6**[7], which is also obtained on heating **4b** to 180°C. The ylides **4a** and **4b** can be protonated with trifluoromethanesulfonic acid in chloroform to give the 1,3-diboretanes **5a** and **5b**, respectively. Reduction of **3** with K/Na alloy in tetrahydrofuran/dimethoxyethane furnishes the radical anion $\mathbf{3}^{\odot\ominus}$ ($a(^{11}B) = 0.58$ mT, $a(^{29}Si) = 3.43$ mT, $g = 2.0024$).

The structure of the compounds **3**—**5** follows from their ^1H-, ^{13}C-, ^{11}B-, ^{31}P-NMR-, and mass spectra[8]; in its IR spectrum, **3** shows an allene band at 1870 cm^{-1}. The shielding of the boron atoms in **4a**, **b** ($\delta(^{11}B) = 61$ and 59, respectively) compared to that in **3** ($\delta = 78$) reflects the delocalization of the negative charge of the ylidic C-atoms ($\delta(^{13}C) = 83.1$ and 81.5, respectively). In the meantime, similar ^{11}B-NMR shifts ($\delta = 51$—58) have been described for dialkylboryltriphenylphosphonium ylides[9]. The ylide structure of **4b** is also supported by the ^{31}P-^{13}C coupling

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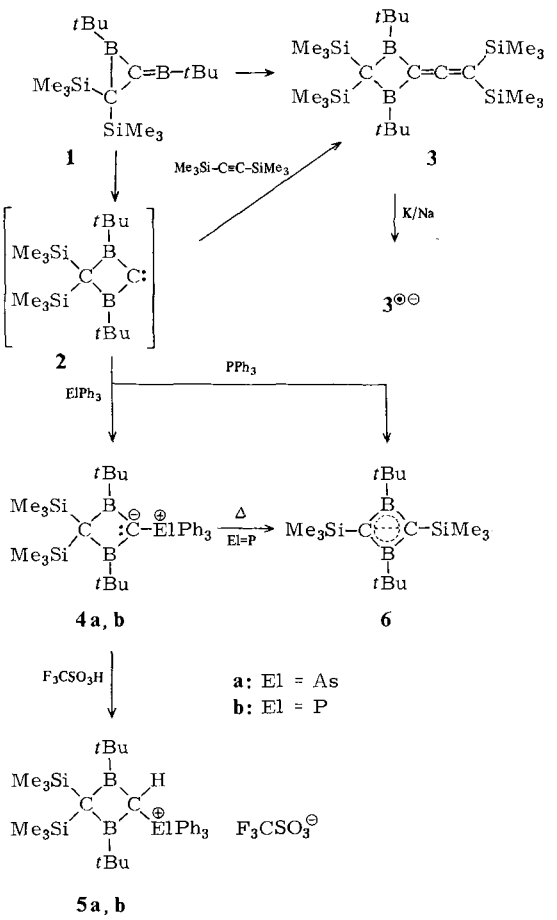
constants of the phenyl C-atoms, which compare with those of other triphenylphosphoranes[10]. The structures of **5a, b** follow from the splitting of the signals of the protonated C-atoms into a doublet and the appearance of two different signals for the trimethylsilyl groups. On cooling,



the ^{13}C-signals of the phenyl groups of **5a, b** become broader[8]; this is indicative of hindered rotation about the C–$\overset{\oplus}{\text{E}}lPh_3$ bond, to our knowledge the first observation of hindered rotation of a triphenylphosphonium- and triphenylarsonium-group.

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CAS Registry numbers:
1, 87556-27-2; **3**, 92396-84-4; **3**$^{\odot\ominus}$, 92396-85-5; **4a**, 92396-78-6; **4b**, 92396-79-7; **5a**, 92396-81-1; **5b**, 92396-83-3

[1] K. Krogh-Jespersen, D. Cremer, J. D. Dill, J. A. Pople, P. von R. Schleyer, *J. Am. Chem. Soc. 103* (1981) 2589.
[2] H. Klusik, A. Berndt, *Angew. Chem. 95* (1983) 895; *Angew. Chem. Int. Ed. Engl. 22* (1983) 877.
[3] Compound **1** possibly has a non-classical structure [4].
[4] P. H. M. Budzelaar, P. von R. Schleyer, K. Krogh-Jespersen, *Angew. Chem. 96* (1984) 809; *Angew. Chem. Int. Ed. Engl. 23* (1984) 825.
[5] This assumption (see H. Klusik, Dissertation, Universität Marburg 1983, p. 107) has in the meantime been confirmed by theoretical calculations [4].
[6] A. J. Speziale, G. J. Marco, K. W. Ratts, *J. Am. Chem. Soc. 82* (1960) 1260; A. J. Speziale, K. W. Ratts, *ibid. 84* (1962) 854.
[7] R. Wehrmann, C. Pues, H. Klusik, A. Berndt, *Angew. Chem. 96* (1984) 372; *Angew. Chem. Int. Ed. Engl. 23* (1984) 372.
[8] **3**: yellow crystals, m.p. 120°C; ^{1}H-NMR ($CDCl_3$): $\delta = 1.08$ (s, 18H, *t*Bu), 0.17, 0.15 (s, each 18H, $SiMe_3$); ^{13}C-NMR ($CDCl_3$, −40°C): $\delta = 195.6$ (s, 1C, sp-C); 83.4 (s, 1C, B–*C*=C, broad), 67.1 (s, 1C, Si–*C*=C), 46.6 (s, 1C, CSi_2, broad), 29.9 (s, 2C, B–*C*Me$_3$, broad), 29.1 (q, 6C, *t*Bu), 4.9, 1.3 (q, each 6C, $SiMe_3$); ^{11}B-NMR ($CDCl_3$): $\delta = 78$; IR (film): $\tilde{\nu} = 1870$ cm^{-1} (C=C=C); MS (28 eV): *m/z* 476 (*M*$^{\oplus}$, 47%), 419 (*M*$^{\oplus}$ − 57, 100).—**4a**: colorless crystals (from $CHCl_3$), decomp. at ca. 125°C; ^{1}H-NMR ($CDCl_3$): $\delta = 7.81-7.34$ (m, 15H, arom. H), 0.68 (s, 18H, *t*Bu), 0.25 (s, 18H, $SiMe_3$); ^{13}C-NMR ($CDCl_3$, −34°C): $\delta = 132.7$, 132.3, 131.2, 128.9 (18C, arom. C), 83.1 (1C, B–C–As, broad), 35.3 (1C, CSi_2, broad), 30.8 (6C, *t*Bu), 23.9 (2C, *C*Me$_3$, broad), 5.7 (6C, $SiMe_3$); ^{11}B-NMR ($CDCl_3$): $\delta = 63$ (36°C, $\nu_{1/2} \approx 1100$ Hz), 58 (91°C, $\nu_{1/2} \approx 500$ Hz).—**4b**: colorless crystals (from $CHCl_3$), decomp. at ca. 180°C; ^{1}H-NMR ($CDCl_3$): $\delta = 7.72-7.39$ (m, 15H, arom. H), 0.62 (s, 18H, *t*Bu), 0.23 (s, 18H, $SiMe_3$); ^{13}C-NMR ($CDCl_3$, −40°C): $\delta = 133.8$ (6C, ^2J(CP) = 9.5 Hz), 131.4 (3C, ^4J(CP) ≈ 0.2 Hz), 130.6 (3C, ^1J(CP) = 87.1 Hz), 128.1 (6C, ^3J(CP) = 11.6 Hz), 81.5 (1C, B–C–P, ^1J(CP) = 84.5 Hz, broad), 36.0 (1C, CSi_2, ^3J(CP) = 32 Hz, broad), 31.0 (6C, *t*Bu), 24.1 (2C, *C*Me$_3$, broad), 6.4 (6C, $SiMe_3$); ^{11}B-NMR ($CDCl_3$): $\delta = 59$ (25°C, $\nu_{1/2} \approx 800$ Hz), 55 (90°C, $\nu_{1/2} \approx 360$ Hz); ^{31}P-NMR ($CDCl_3$): $\delta = 4.9$; MS (28 eV): *m/z* 553 (*M*$^{\oplus}$ − CH_3, 13%), 511 (*M*$^{\oplus}$ − *t*Bu, 100).—**5a**: ^{1}H-NMR ($CDCl_3$): $\delta = 7.82-7.58$ (*m*, 15H, arom. H), 2.90 (s, 1H, H–C–As), 0.81 (s, 18H, *t*Bu), 0.46, 0.39 (s, each 9H, $SiMe_3$); ^{13}C-NMR ($CDCl_3$, −38°C): $\delta = 134.0$ (3C), 132.1, 130.6 (each 6C), 125.4 (3C, broad), 118.1 (q, 1C, CF_3, ^1J(CF) = 317 Hz), 64.0 (1C, CSi_2, broad), 33.6 (d, 1C, H–C–As, ^1J(CH) = 116 Hz, broad), 28.7 (6C, *t*Bu), 27.5 (2C, *C*Me$_3$, broad), 6.1, 4.5 (each 3C, $SiMe_3$); δ(^{11}B) not determinable due to line width of 1600 Hz.—**5b**: ^{1}H-NMR ($CDCl_3$): $\delta = 7.74-7.59$ (m, 15H, arom. H), 2.85 (d, 1H, H–C–P, ^2J(PH) = 21 Hz), 0.69 (s, 18H, *t*Bu), 0.42, 0.40 (s, each 9H, $SiMe_3$); ^{13}C-NMR ($CDCl_3$): $\delta = 134.9$ (d, 3C, ^4J(CP) = 3.0 Hz, at −34°C broad), 133.4 (d, 6C, ^2J(CP) = 9.5 Hz, at −34°C broad), 130.1 (d, 6C, ^3J(CP) = 12.5 Hz), 122.4 (d, 3C, C–P, ^1J(CP) = 102 Hz, broad), 118.6 (q, 1C, CF_3, ^1J(CF) = 318 Hz), 65.0 (d, 1C, CSi_2, ^3J(CP) = 21 Hz, −34°C, broad), 34.0 (dd, 1C, H–C–P, ^1J(CP) = 43 Hz, ^1J(CH) = 110 Hz, −34°C, broad), 28.9 (6C, *t*Bu), 27.7 (2C, *C*Me$_3$, −34°C, broad), 6.5, 5.0 (each 3C, $SiMe_3$); ^{31}P-NMR ($CDCl_3$): $\delta = 19.0$; δ(^{11}B) not determinable due to line width of 1600 Hz.
[9] H. J. Bestmann, T. Arenz, *Angew. Chem. 96* (1984) 363; *Angew. Chem. Int. Ed. Engl. 23* (1984) 381.
[10] T. A. Albright, W. J. Freeman, E. E. Schweizer, *J. Am. Chem. Soc. 97* (1975) 940.

BOOK REVIEWS

Chemical Research Faculties. An International Directory. American Chemical Society, Washington DC 1984. xxxv, 407 pp., bound, $ 129.95 (USA and Canada), $ 155.95 (all other countries).

This book, sister volume to the excellent *ACS Directory of Graduate Research 1983,* which surveys chemical research faculties (names of institutions, lists of faculty members, etc.) in the USA and Canada, purports to supply analogous information about faculties in the rest of the world. With this aim, source data were collected from 62 countries, and the names of 9,900 faculty members from 737 departments are included. Information is organized according to country, institution, and by an alphabetical listing of the respective faculty members. Inclusion of cross indexes facilitates location of individual researchers in a given area of chemistry. Additionally, a statistical survey of the numbers of academic staff, research workers, and of masters' and doctoral degrees awarded for the academic years 1980—81 and 1981—82 is presented on an institutional basis in tabular form. Since data collection for

the volume began in August 1982, entries are probably only accurate up to this date.

Alone the collection of such a vast amount of data presents a difficult task to the editorial staff involved; publication of a compendium of research faculties around the world that could be of real value to the chemical community is a problem which assumes gargantuan proportions. Clearly not every chemical research institution can be covered. What is required is the judicious selection of institutions, comprehensive coverage of those selected, and a critical appraisal to guard against the omission of reputable scientists from smaller institutions.

Unfortunately, however, it would appear that the zeal to appear in print rather than to provide a balanced, fairly comprehensive reference volume has been the guiding principle in publishing *Chemical Research Faculties 1984*. With the exception of its treatment of the English-speaking world, which is acceptable, coverage of research faculties in the rest of the world falls well short of expectations. The book's particularly disappointing coverage of continental European research institutions is conspicuous. By its omission, one can only assume, for example, that the editors are unaware that the ETH Zürich has a chemistry faculty! Other institutions which fail to get a mention are too legion to list individually; suffice it to say that of the ca. 50 chemical institutions in the Federal Republic of Germany only 21 appear. And of those, only a skeleton faculty appears in many instances: according to the information presented, the chemistry faculty of the Universität Heidelberg has only one member! Similar fates are suffered, inter alia, by many chemical research faculties in France, Italy, and Spain.

In summary, this book falls well short of providing a well-balanced, useful directory for the scientific community and in no way justifies its extremely high cost. One hopes that the shortcomings delineated here will be improved in a 2nd edition, for there is certainly a need for a comprehensive reference work of this type.

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Das Nitrosamin-Problem. Edited by *R. Preussman*. A publication of the Deutsche Forschungsgemeinschaft. Verlag Chemie, Weinheim 1983. xi, 326 pp., paperback, DM 75.00.

This book quotes the detailed final reports of 30 scientists participating in the DFG program "Analysis and Formation of *N*-Nitroso Compounds". Because of the importance of nitrosamines as possible carcinogens, about five million DM have been made available for this research over the last ten years. As a result of this intensive support, suitable measures have been discovered for reducing their formation, thus allowing the prejudice of the human organism to be lessened.

The individual reports have been assembled into ten chapters. Each theme is introduced in a review by an expert. This concept guarantees that both a comprehensive general presentation of the problems and a more detailed treatment of specific questions is offered to the reader.

K. Heyns devotes his introductory remarks to a history of the "nitrosamine problem" and reviews the present state of research. The determination of very low concentrations of these carcinogens in foods was, as is reported on by *G. Eisenbrand*, only possible after the development of a highly sensitive and specific method. From the review by *B. Spiegelhalder* it can be seen that carcinogenic nitrosamines are not only detectable in foods but also in other requisites, medicaments, tobacco and tobacco smoke as well as in the air of various industrial plants.

The first routine findings from foodstuff monitoring are reported by *R. Frommberger* and *H. Allmann* for the Federal Republic of Germany and by *G. Ellen* and *P. L. Schuller* for the Netherlands.

A solution of the "nitrosamine problem" is only possible with the possession of an extensive knowledge of the chemistry and the formation of these substances. These questions are treated by 13 authors in two voluminous chapters (ca. 150 pages).

As the review articles of *G. Eisenbrand* and *R. Loeppky* make clear, preventative measures could greatly reduce the exposure of our bodies to nitrosamines.

However, because of the widespread occurrence of amines and nitrites—that is, the precursors of nitrosamines—in the environment it is impossible to avoid the formation and intake of small quantities of these carcinogenic substances. This makes the remarks of *R. Preussmann* concerning the biological effect of *N*-nitroso compounds worthy of particular attention.

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Copper Coordination Chemistry: Biochemical and Inorganic Perspectives. Edited by *K. D. Karlin* and *J. Zubieta*. Adenine Press, Guilderland 1983. 488 pp., bound, $ 69.00.

This book is a summary of the "1st Conversation in Copper Coordination Chemistry" held at Albany State University from the 1st to the 4th of June 1982. It presents a series of investigations concerning the role of copper in biological and inorganic electron transport processes and in general catalysis, as well as new developments concerning the chemistry of Cu^{I} and Cu^{II} complexes with nitrogen- and oxygen-containing ligands. The two editors wish to use this volume to effect a connection between classical inorganic chemistry and biology. Bioinorganic chemists seek to gain an insight into the complicated and multifaceted activities of proteins and enzymes by investigating the structural and electronic properties of their active centers. Chemical and spectroscopic investigations of simple, low molecular weight model complexes yield vital information when compared with the corresponding high molecular weight biologically active substances.

In his introductory survey *E. Solomon* characterizes known Cu-enzymes and -proteins according to spectroscopic criteria and emphasizes the necessity of working out the basics using inorganic complexes. Absorption transitions in the UV/VIS range, EPR, CD, and MCD as well as the relatively new EXAFS spectroscopy were amongst the spectroscopic techniques which found application here as well as in the following contributions.

An EXAFS evaluation of the binuclear bonding center of several derivatives of arthropod and mollusc haemocyanins by *T. G. Spiro* et al. begins the first section of the book, which summarizes investigations of spectroscopy, kinetics, structure and redox behavior. These include the

steric and electronic influence of various ligands on coordination at Cu^{I} and Cu^{II} and on the Cu^{I}/Cu^{II} potential. Alongside the methods already mentioned results obtained by X-ray structural determinations, cyclovoltammetry, coulometric and potentiometric measurement and MO calculations are also discussed.

The second part of the book is devoted to the behavior of O_2 and of CO bound to Cu^{I} and Cu^{II}. The catalytic role in the oxidation of organic substrates with molecular oxygen is treated in detail. Copper compounds are involved in electron transfer reactions and serve to activate oxygen.

The book provides a comprehensive coverage of the current status of investigations into the structure/function relationships of Cu^{I} and Cu^{II} coordination complexes—binuclear ones in particular. The literature is covered up to and including 1982. There is no appended list of ligands discussed which would be an aid to gaining a general picture. Unfortunately, the biochemical perspectives mentioned in the title are on the whole limited to the first two contributions. Afterwards biochemical problems are virtually only alluded to in the various introductions.

This book offers a wealth of information to the chemist or physicist who works with model systems. It can be recommended to the functionally interested biochemist as a reference work. It is also of use to the advanced student who wishes to familiarize himself with coordination complex-oriented bioinorganic chemistry.

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Handbuch der photometrischen Analyse organischer Verbindungen. By *B. Kakáč* and *Z. J. Vejdělek*. Verlag Chemie, Weinheim. Band 1 (1974): viii, 718 pp., bound; Band 2 (1974): vi, 598 pp., bound; together DM 360.00. 1st supplementary volume (1977): xxv, 464 pp., bound, DM 138.00. 2nd supplementary volume (1983): xxxi, 506 pp., bound, DM 198.00.

Nowadays there are so many instrumental molecular spectroscopic techniques (e.g. UV, IR, Raman and fluorescence spectroscopy) and mass spectroscopic methods available for the identification and determination of organic substances, mainly used in combination with TLC, GC or HPLC that photometric methods based on color reactions may seem a little antiquated. However, this is quite untrue. The large response to the original two-volume handbook on photometric analysis, which first appeared in 1974, has stimulated the authors and publishers to bring out supplements about every five years. The two supplementary volumes covering the literature from 1970 to 1975 and 1975 to 1980, are scarcely smaller in extent than the main volumes covering the literature up to 1970. As before, chemical reactions of organic compounds leading to photometrically determinable coloration have an important, and possibly increasingly important, place in many areas of analytical laboratory practice (e.g. biochemistry, biology, medicine, pharmacy, food chemistry). This is now particularly the case for microliter scale reaction volumes (flow injection technique) and for photometric detection systems for the very powerful HPLC methods, which allow the determination of more and more classes of organic compounds economically at very low concentrations. From this point of view, this carefully compiled systematic review of the color reactions of organic compounds is a valuable aid. Principles, reaction mechanisms, reaction conditions, absorption maxima, selectivity, avoidance of interference and exact instructions for carrying out the determinations are very clearly outlined for 18 classes of compounds according to the Beilstein system, and are easily traceable because of the comprehensive reagent, author and subject indices. In order to find a particular photometric method for a chosen organic compound, the reader requires the subject indexes of all four volumes that have been published up to now, but this does not cause any problems because the whole work is systematically organized.

The following classes of substance are treated in both supplementary volumes: unsaturated hydrocarbon compounds, hydroxy compounds, thiols and related compounds, keto compounds, carboxylic acids and their derivatives, organic sulfates and sulfonates, amino compounds, hydroxylamines, hydrazine compounds, azo and diazo compounds, nitro and nitroso compounds, halogen compounds, organic compounds of metals and of non-metals, nitrogen-free heterocyclics, nitrogen-containing heterocyclics, carbohydrates and their derivatives, amino acids, peptides and proteins, as well as steroids and related compounds.

Unfortunately, the work only covers the determination of organic compounds, so that the reactions of the ions of elements are only dealt with from this viewpoint. An exception is the section dealing with organic compounds of metals and non-metals, which is very valuable for methods of determining organo-element compounds (e.g. of Hg, Sn, Pb, As) particularly in environmental analysis.

The value of this work lies principally in its thorough literature coverage, which is not limited to the normal analytical journals, but also includes the partially inaccessible literature of the neighboring disciplines (such as pharmacy, medicine and food chemistry), and in the critical choice of important substances and methods, which are described in detail. For less important topics, it is necessary to refer back to the original literature.

This synoptic, clearly written handbook, which is kept up-to-date by the supplementary volumes, should be of interest to a large number of scientists of differing disciplines who have to analyze organic compounds of synthetic and natural origin in a wide variety of different matrices. For this reason, this book ought to be obligatory for every analytical chemistry library, despite its high cost, which is justified by the content and the production.

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Heteropoly and Isopoly Oxometalates. By *M. T. Pope*. Springer-Verlag, Berlin 1983. xiii, 180 pp., bound, DM 124.00.

The chemistry of the polyoxoanions of the transition metals occupies an important intermediary position between solid state chemistry and the chemistry of aqueous solutions. This fact is emphasized in this book which has been published as Volume 8 of the series "Inorganic Chemistry Concepts". A competent authority provides a comprehensive review of the chemistry, structure, possible applications and future trends of this class of compounds. The state of knowledge in this classical field of inorganic chemistry has developed rapidly since the last monograph devoted to it, *P. Souchay*'s "Ions Minéraux Condensés",

was published at the end of the 1960s. The roots of the field stretch back into the last century and the first climax, reached in 1920 by *Rosenheim*, was soon built upon. This was a result of the contribution of newer methods, such as the wide availability of X-ray methods for the determination of solid state structures or ^{17}O-, ^{91}V-, ^{95}Mo-, and ^{183}W-NMR spectroscopy in solution. Accordingly, this book begins with a description of the methods of investigation, their scope and their limits. A further introductory chapter deals with the synthetic methods in aqueous and non-aqueous solutions, with the most important structural types, and with applications in biochemistry and catalysis.

The two sections of 24 and 33 pages concerning the isopolyanions of the elements V, Nb, Ta, Mo, and W and their heteropolyanions constitute the main part of the book and are laid out according to the coordination number of the heteroatom. The author limits himself essentially to compounds with "finite" structures and to species that exist in solution. The complex structures are explained using easily understood language; reactions between individual species are presented in clear graphics. The diagrams of the structures, which have been drawn with great artistic skill by *Howard T. Evans Jr.* are a valuable contribution as well as being aesthetically pleasing.

Two further chapters are dedicated to the specific properties of heteropolyanions: a) to the metal complexes: polyanions themselves or species derived from them having open structures can function as ligands or cryptands; b) the redox chemistry and electronic structure of reduced polyanions: recent developments are reviewed here for the first time. Chapter 7 treats polyanions with covalently bound organic groups. Interest in this type of compound has recently increased in connection with their being viewed as models for heterogeneous catalysis. Amongst the topics dealt with by the author in the last section are the ability of other elements to act as addenda in polyoxometalates (e.g. Sb^{IV}, Te^{VI}, I^{VII}) or to replace oxygen (e.g. fluorine or sulphur).

Y. Yeannin and *M. Fournier* develop rules for a systematic nomenclature of this class of compound in an appendix; this will be of particular value for literature searches. The three indexes at the end of the book are exemplary; they are a list of 771 references including publications up to the beginning of 1982, an author index, and finally a general index containing almost 400 headings. The clear construction of this book and its excellent contents guarantee a rapid synopsis not just to inorganic chemists. It should be in every library.

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Guide to Lehninger's Principles of Biochemistry with Solutions to Problems. By *P. van Eikeren*. Worth Publishers, New York 1984. 544 pp., Paperback, $ 12.95.—ISBN 0-87901-178-5

Plasma Chromatography. Edited by *T. W. Carr*. Plenum Publishing Corporation, New York 1984. xiii, 259 pp., bound, $ 37.50.—ISBN 0-306-41432-5

Advances in Infrared and Raman Spectroscopy. Vol. 11. Edited by *R. J. H. Clark* and *R. E. Hester*. John Wiley, Chichester 1984. xix, 383 pp., bound, £ 49.50.—ISBN 0-471-26267-6

Handbook of Particle Sampling and Analysis Methods. By *C. H. Murphy*. Verlag Chemie International, Deerfield Beach, Florida 1984. xiv, 354 pp., bound, DM 165.00.—ISBN 0-89573-116-9

Chemical Reactor Design and Operation. 2nd edition. By *K. R. Westerterp, W. P. M. van Swaaij*, and *A. A. C. M. Beenackers*. John Wiley, Chichester 1984. xxxii, 767 pp., bound, £ 49.50.—ISBN 0-471-90183-0

1,3-Dipolar Cycloaddition Chemistry. Vols. 1 and 2. Edited by *A. Padwa*. John Wiley & Sons, Chichester 1984. Vol. 1: xiii, 817 pp., bound, Vol. 2: xiii, 704 pp., bound, together £ 292.00.—ISBN 0-471-08364-X

Identification and Analysis of Organic Pollutions in Air. Edited by *L. H. Keith*. Butterworth Publishers, London 1984. xxi, 486 pp., bound, £ 55.00.—ISBN 0-250-40575-X

Große Naturforscher. Vol. 45: Otto Hahn. Ein Forscherleben unserer Zeit. By *W. Gerlach* and *D. Hahn*. Wissenschaftliche Verlagsgesellschaft, Stuttgart 1984. 278 pp., bound, DM 39.00.—ISSN 0072-7741

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Cyclic Voltammetry—"Electrochemical Spectroscopy"

New Analytical Methods (25)

By Jürgen Heinze*

Polarography is still the best known classical measuring method in electroanalytical chemistry. However, in recent years its position has been challenged by cyclic voltammetry (CV). Simple diagnostic criteria and relatively easily acquired measuring techniques have hastened this development. Cyclic voltammetry has the further attraction of providing information not only on the thermodynamics of redox processes but also on the kinetics of heterogeneous electron-transfer reactions and coupled chemical reactions. The characteristic shapes of the voltammetric waves and their unequivocal position on the potential scale virtually fingerprint the individual electrochemical properties of redox systems. For this reason the method has been labeled "electrochemical spectroscopy".

1. Introduction

Chemical research has only recently reacted to the fact that chemical reactions very often involve electron-transfer processes[1–3]. Recognition has been slow probably because of the widely held view that electron-transfer processes were purely thermodynamic phenomena, which, e.g., the electrochemist interpreted, with the aid of the Nernst equation, as redox equilibria. The kinetics of electron-transfer processes went virtually unrecognized. Accordingly, electrochemistry, as the science of the properties of charge carriers in condensed matter, was long regarded as a domain of thermodynamics. The electrode was solely a probe for measuring equilibrium potentials.

This view changed fundamentally once it became clear that electron-transfer processes, whether homogeneous or heterogeneous, have, on the one hand, a finite rate whose value is dependent on the activation parameters[4–6] and, on the other, that they are often preceded and followed by chemical reactions[7–9]. Thus, in electrochemistry the methodical emphasis gradually shifted from the static determination of potentials to the dynamic determination of current.

Numerous dynamic methods in electroanalytical chemistry have been developed in recent decades. Of these, cyclic voltammetry (CV) has gained the greatest popularity[10]. It has already largely supplanted classical polarography—except for purely analytical problems. Its applications range from the study of simple redox processes in organic and inorganic chemistry to the characterization of multielectron-transfer processes in biochemistry and macromolecular chemistry.

There are two main reasons for this development. An exact mathematical analysis of the theoretical basis of the method has existed for the past 15—20 years. Hence, it has been possible to provide a quantitative interpretation of all the important variants of electrochemical processes in terms of their voltammetric response[11–18]. Moreover, modern numerical methods facilitate calculation of voltammetric curves for complex electrochemical processes[19,20]. A second consideration has been decisive for the popularity of the method: With the aid of a few simple diagnostic criteria, it is possible to obtain, even without complicated mathematics, a fair amount of information on the electrochemical properties of the species being studied[21–23].

The available data do not refer only to thermodynamic parameters such as, e.g., the redox potential; the CV experiment also provides direct insights into the kinetics of electrode reactions, which include both heterogeneous and homogeneous electron-transfer steps as well as coupled

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chemical reactions. The determination of reactive intermediates and their kinetic analysis promise to become major applications of cyclic voltammetry together with the characterization of the thermodynamics of redox systems.

Furthermore, voltammetry is increasingly being used as a technique of studying all types of potential-dependent interfacial process. These include, inter alia, adsorption processes[24,25], electrocrystallization phenomena[26,27], and charge-transfer reactions at semiconductor electrodes[28,29] or between nonmiscible electrolytes[30].

2. Experimental Basis

Normally, routine voltammetric experiments are performed using a stationary working electrode in a quiet solution. Starting from an initial potential E_i, a linear potential sweep (potential ramp) is applied to this electrode. After reaching a switching potential E_λ, the sweep is reversed and the potential returns linearly to its initial value. Although it is technically possible to generate sweep rates, $v = dE/dt$ [V/s], of up to 10000 V/s, in practice the rate lies between 5 mv/s and 1 V/s, with a maximum of 3000 V/s under favorable conditions. The sweep rate is one of the most important variables in voltammetry, for it controls the time scale of the experiment.

In cyclic voltammetry, mass transport of the reducible or oxidizable electroactive species occurs only by diffusion. Thus, in order to avoid migration currents and ensure conductivity, a ca. 0.1 M solution of a ground or supporting electrolyte is added to the solution. Alkali metal and especially tetraalkylammonium salts have proved the most effective. The latter can also be used in aprotic solvents and some, e.g. tetra-*n*-butylammonium hexafluorophosphate [TBA]PF_6 (Fig. 4), are characterized by extraordinarily high decomposition voltages. The concentrations of the electroactive substance normally lie between 10^{-3} and 10^{-5} M.

Besides the Faradaic current based on the heterogeneous charge transfer at the phase boundary, there is also a capacitive current from the charging of the electrochemical double layer without charge transfer between electrode and electrolyte. This is measured with suitable equipment and recorded as a characteristic current-voltage curve—a cyclic voltammogram (Fig. 1).

As it is impossible to monitor absolute single electrode potentials, the working electrode (WE) potential E always refers to a nonpolarized reference electrode (RE), e.g. Ag/AgCl or the saturated calomel electrode (SCE). If the currents are low and the solvent-electrolyte system has a high conductivity, this type of two-electrode cell is sufficient for voltammetric measuring. Its use is well-known from classical polarography[31-33].

For large currents and/or a low-conductivity solution, such as, e.g., is the case with aprotic solvents, the applied voltage is no longer identical to the desired real potential at the working electrode. With current $i(t)$ in the system, the internal resistance of the electrolyte causes an additional drop in potential, so that the WE potential $E(t)$ will be smaller than the applied cell voltage $E_{appl}(t)$ by an amount corresponding to the Ohmic potential drop (iR-drop) [Eq. (1)].

$$E(t) = E_{appl}(t) - i(t)R \qquad (1)$$

In addition, large currents, as observed at high sweep rates, destroy the reference electrode.

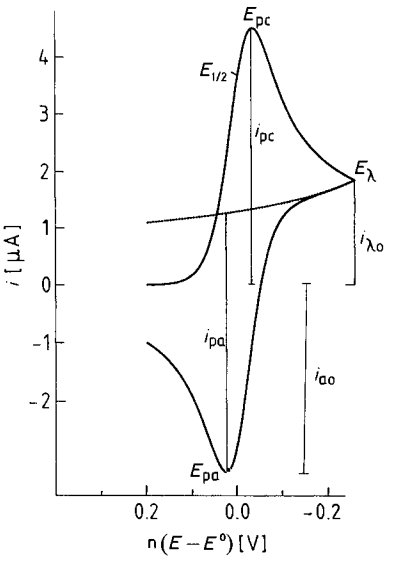


Fig. 1. Cyclic voltammogram for a reversible charge transfer; E_{pc}: cathodic peak potential, E_{pa}: anodic peak potential, E_λ: switching potential, $E_{1/2}$: half-wave potential, i_{pc}: cathodic peak current, i_{pa}: anodic peak current, $i_{\lambda o}$: current at E_λ, i_{ao}: anodic peak current at baseline.

Both effects can be largely avoided by using potentiostats together with a three-electrode cell arrangement[25,34-36]. In this technique current is passed through the working and an additional auxiliary electrode (AE), while almost no current flows through the RE on account of its high impedance. In order to keep the existing uncompensated iR-drop as small as possible, the reference electrode is placed as close as possible to the WE using a Luggin's capillary. Potentiostatic control ensures that the real potential $E(t)$ at the WE with respect to the RE is, by and large, the same as the applied cell voltage generated by the function generator. Operational amplifiers in the control circuit adjust the current passing through the WE and AE until the potential $E(t)$ corresponds to E_{appl}.

Besides potentiostats with the electrochemical cell arrangement, the standard device for voltammetric experiments comprises a voltage scan generator, which supplies the desired potential program, as well as an XY recorder (or a suitable fast transient recorder) which registers the current-voltage curve (Fig. 2). Suitable equipment, mostly in the form of modular systems, is commercially available.

For the study of reductions, mercury has proved to be the material of choice for the WE. It is used in voltamme-

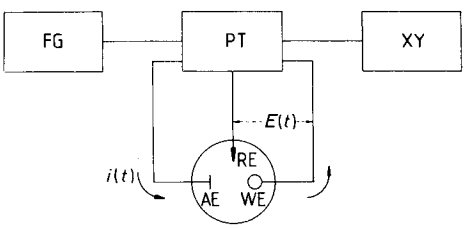


Fig. 2. Schematic experimental setup for cyclic voltammetry; FG: voltage scan generator, PT: potentiostat, XY: recorder, WE: working electrode, RE: reference electrode, AE: auxiliary electrode.

try as a stationary hanging mercury drop electrode (HMDE) and is superior to all other materials for experiments in aqueous solutions because of its high hydrogen overpotential. But mercury also has certain advantages in aprotic solutions since its surface can be reproduced at will. For anodic measurements above +0.4 V vs. Ag/AgCl (mercury is oxidized!) as well as for other special purposes, solid electrodes have to be used, preferably of an inert material such as platinum, gold, or graphite[22]. In this case, however, it is often difficult to clean the electrode surfaces.

Optimal preparation of the samples, the electrolytic solution, and the measuring cell are essential for the success of the experiments. Impurities, even in traces, can considerably impair the quality of the cyclic voltammograms. In aqueous solutions usually only oxygen, reducible in the range −0.2 to −0.8 V vs. SCE, must be removed from electrolytic solutions, prepared under standard analytical conditions. The requirements for aprotic solvents are far more stringent, affecting both the purification of the solvent and the preparation of the samples. The main problem lies in removing protic impurities, principally water. Numerous techniques have been developed for purifying organic solvents for use in voltammetric measurements[37–41], and *Coetzee* has published a survey in a recent IUPAC monograph[42].

Careful purification of solvents together with a standard sample preparation technique, as practised by various research groups, produces a solvent-electrolyte system which, in electrochemical jargon, is "waterfree"[35,43–45]. However, it is impossible to remove all traces of water from the walls of the cell and the supporting electrolyte. Thus, on the one hand, the available potential range is smaller than theoretically possible and, on the other, reactive ions formed at the electrode undergo follow-up reactions. *Hammerich* and *Parker*[46] developed a very elegant solution to this problem by directly adding superactive alumina to the voltammetric cell, thereby creating a superdry medium.

This method is not always suitable when sensitive materials are being studied or for quantitative measurements, particularly spectroscopic experiments. More recently, cells and equipment have been developed which avoid direct contact between the solvent-electrolyte system and the alumina *during* the voltammetric experiment, without impairing efficiency[47–49].

Figure 3 is a schematic representation of such an analytical cell. The drying procedure is as follows: the already highly purified solvent is transferred by distillation under high vacuum from the voltammetric cell, which already contains the supporting electrolyte, to superactive alumina in a separate vessel and then similarly returned to the voltammetric cell. By means of this procedure, the protic impurities on the glass walls of the cell and in the supporting electrolyte are "extracted" into the solvent and then adsorbed onto the alumina. A voltammetric background curve for superdry propionitrile is shown in Figure 4. The available potential range in this case is more than 6.5 V. The vacuum-condensation method cannot always be used with high boiling solvents or other low volatile additives (e.g. complexing agents). A cell with an integrated alumina

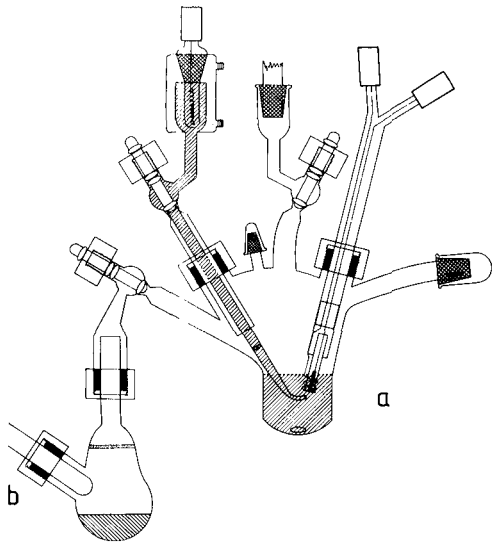


Fig. 3. Electrochemical cell for voltammetric experiments under "superdry" conditions: a) measuring cell with three-electrode arrangement; b) drying vessel with superactive alumina (Woelm, ICN Super I).

tube developed by *Kiesele*[49] has proved extremely efficient in such cases. Voltammetric measurements under superdry conditions are often an essential prerequisite for the quantitative evaluation of experimental data.

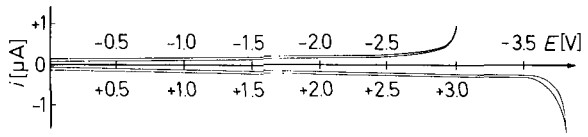


Fig. 4. Background curve ($v = 50$ mV/s) for proprionitrile/[TBA]PF_6 vs. Ag/AgCl.

3. Electrode Reactions in the CV Experiment

3.1. Simple Electron Transfer: E Mechanism

The simplest Faradaic electrode reaction is the heterogeneous charge transfer from an electroactive species **A** to the electrode or vice versa, in which, dependent on the given electrode potential, **A** is either oxidized or reduced to **B** (electron-transfer mechanism: E mechanism[50]).

$$\mathbf{A} \pm e \overset{E}{\rightleftharpoons} \mathbf{B} \tag{2}$$

In order to simplify the theoretical analysis, only reduction processes will be discussed. Two processes determine the shape of the voltammetric current-voltage curve. These are heterogeneous charge transfer and diffusional mass transport. The heterogeneous charge-transfer at the electrode interface is described by the Butler-Volmer equation [Eq. (3)], the basic equation in electrochemical kinetics[4].

$$j_A(0,t) = \frac{i}{nFA} = C_A(0,t)k^0 \exp\left[-\alpha \frac{nF}{RT}(E-E^0)\right] - C_B(0,t)k^0 \exp\left[(1-\alpha)\frac{nF}{RT}(E-E^0)\right] \tag{3}$$

where k^0 = heterogeneous standard rate constant,
α = transfer coefficient,
E^0 = standard potential,
A = electrode area,
j = flux at the electrode interface, F = Faraday constant.

In accordance with Eq. (3), the heterogeneous flux, i.e. the measurable current density, depends on the surface concentrations of the redox partners involved, the actual electrode potential $E(t)$, and the heterogeneous standard rate constant k^0. The standard potential E^0 characterizes a situation in which the surface concentrations of the oxidized and reduced forms are equal under conditions of *thermodynamic* equilibrium. Because of the difference between the resulting potential-dependent surface concentrations $C_A(0,t)$ and $C_B(0,t)$ and the concentrations in the rest of the solution, a gradient emerges, along which diffusion-controlled mass transport occurs. The time-dependent concentration distribution in the expanding diffusion layer can be derived from Fick's 2nd law [Eq. (4)].

$$\frac{\partial c_i}{\partial t} = D_i \frac{\partial^2 c_i}{\partial x^2} \tag{4}$$

where i = **A**, **B**

Eq. (4) holds only for purely linear semi-infinite diffusion, a situation which does, in fact, apply in most cases. In the case of smaller electrode areas, $A \leq 1 \cdot 10^{-6}$ m^2 (such as, e.g., the hanging mercury drop electrode), the diffusion equations must be modified to take account of the spherical or other shape of the electrode[51,52].

If voltammetry is used for analytical purposes, an extremely large electrode area/volume ratio is often chosen to increase sensitivity, e.g., in inverse voltammetry or when working with thin-layer cells. Under these conditions, diffusion is no longer semi-infinite but finite, i.e. the thickness of the diffusion layer is limited by the volume, and this changes the characteristics of the diffusion gradient[53,54].

The concentration gradient at the electrode surface is directly proportional to the charge flux [Eq. (5)].

$$j_A(0,t) = -D_A \left(\frac{\partial C_A}{\partial x}\right)_{x=0} = D_B \left(\frac{\partial C_B}{\partial x}\right)_{x=0} \tag{5}$$

Comparison of Eqs. (3) and (5) shows that the measurable current at the WE has two components; one for the heterogeneous charge transfer and one for the mass transport. However, there are two exceptions: the reversible and the irreversible cases.

1. *Reversible Case:* $k^0 > 10^{-1}$ cm/s

The rate of heterogeneous charge transfer is so high that a dynamic equilibrium is established at the phase boundary. The Butler-Volmer equation [Eq. (3)] is reduced to the Nernst equation, i.e. the surface concentrations $C_A(0,t)$ and $C_B(0,t)$ depend only on the actual electrode potential and are no longer influenced by heterogeneous kinetic effects. This case is termed reversible (Fig. 5a) because a thermodynamic equilibrium exists at the phase boundary. The current, as a measurable quantity for the charge flux at the electrode surface, is influenced solely by the mass transport, the slowest step (diffusion control). The characteristic shape of the cyclic voltammogram is a result of the potential-dependent changes in the surface concentrations of the redox system and the simultaneous diffusion processes. The surface concentration of the reactant **A** decreases and that of **B** increases with the time-dependent potential $E(t)$. Simultaneously, and as a consequence, the gradient and, hence, also the charge flux increase, until the E_0 potential has been exceeded and the surface concentration of **A** becomes negligible. The current reaches a maximum ($\rightarrow i_p$) and the diffusion layer continues to expand, as a result of which the concentration gradient at the electrode surface decreases virtually independently of the actual potential. The current curve decays. Analogous phenomena occur in the opposite potential direction. The reverse flux direction, the result of the potential-dependent conversion of **B** into **A**, produces a corresponding negative current which reaches a corresponding minimum value and then slowly decays as the species **B** in the diffusion layer is used up.

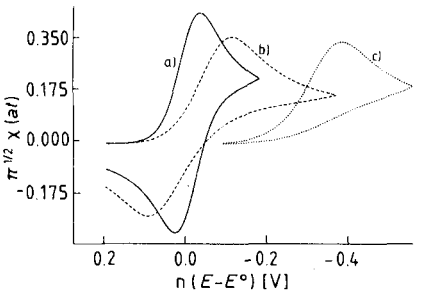


Fig. 5. Cyclic voltammograms for a) the reversible (—, $k^0 = 1$ cm/s), b) the quasi-reversible (– – –, $k^0 = 1.25 \cdot 10^{-3}$ cm/s), and c) the irreversible charge transfer (· · ·, $k^0 = 6.25 \cdot 10^{-6}$ cm/s); $D = 1 \cdot 10^{-5}$ cm^2/s, $v = 0.1$ V/s, $\pi^{1/2}\chi(at)$: normalized current function [16], dimensionless.

2. *Irreversible Case:* $k^0 < 10^{-5}$ cm/s

Charge transfer at the electrode is extremely slow. Depending on the potential, only one of the cathodic and anodic heterogeneous reactions has a measurable rate. Thus, the current is largely controlled by the rate of the charge-transfer reaction (charge-transfer control). Since the surface concentrations at the electrode are dependent on the heterogeneous reaction and are far removed from thermodynamic equilibrium, one speaks of an irreversible process (Fig. 5c). Under such conditions, the Nernst equation does not apply. Furthermore, this means that the measured potential values cannot be compared with thermodynamic equilibrium potentials.

3. *Quasi-reversible Case:* $10^{-1} > k^0 > 10^{-5}$ cm/s

Both the charge transfer [Eq. (3)] and the mass transport [Eqs. (4), (5)] determine the current. The Nernst equation is only approximately satisfied. The charge transfer is therefore termed quasi-reversible (Fig. 5b).

The special feature of voltammetry is that the properties of the redox system itself do not predetermine which of the three cases will occur. The time scale of the CV experiment can be varied over a wide range using the sweep rate.

This permits electrode reactions to be steered out of the range of charge-transfer control into that of diffusion control and vice versa. Depending on which of the two components dominates in the electrode processes, the corresponding characteristics are reflected in the cyclic voltammetric curve. In practice, under standard measuring conditions reversible and quasi-reversible cases occur most frequently.

Over the last twenty-five years appropriate theoretical analyses have been published[11-16]. In analytical approaches the diffusion equation (4) is transformed into an integral equation which takes into account the initial and boundary conditions [Eq. (3) and (5)] and is then solved either numerically or by series expansion. The best known studies are those of *Nicholson* and *Shain*, whose nomenclature has generally been adopted in the literature. Tables can be compiled for the theoretically determined current function $\pi^{1/2}\chi(at)$ in the reversible case (Table 1). Using this function together with the assigned experimental parameters in accordance with Eq. (6), one can calculate the cyclic voltammetric curves[16].

$$i = \mathrm{n}FA\, C_{\mathrm{A}}^{*}\,(D_{\mathrm{A}}\, a)^{1/2}\pi^{1/2}\chi(at) \tag{6}$$

where $at = \dfrac{\mathrm{n}Fvt}{RT} = \dfrac{\mathrm{n}F}{RT}(E(t) - E_{\mathrm{i}})$

and C_{A}^{*} = substrate concentration the electrolyte

Table 1. Computed current functions [177] in the voltammetric experiment for reversible charge-transfer.

$(E-E_{1/2})$n [mV]	$\pi^{1/2}\chi(at)$	$(E-E_{1/2})$n [mV]	$\pi^{1/2}\chi(at)$
120	0.0092	− 10	0.4188
100	0.0198	− 15	0.4320
80	0.0418	− 20	0.4408
60	0.0849	− 25	0.4454
40	0.1610	− 28.5	0.44629
30	0.2125	− 30	0.4461
28.5	0.22315	− 35	0.4435
25	0.2408	− 40	0.4380
20	0.2701	− 50	0.4210
15	0.2995	− 60	0.3992
10	0.3283	− 80	0.3530
5	0.3555	−100	0.3125
0	0.3801	−120	0.3803
−5	0.4014	−150	0.2449
		−200	0.2074

It transpires that to study simple electron-transfer reactions so-called diagnostic criteria are often sufficient to obtain qualitative and quantitative information about thermodynamic and kinetic properties of the system, without having to analyze the entire cyclic voltammogram. The most important quantities are the two peak potentials E_{pc} and E_{pa} as well as the assigned peak currents i_{pa} and i_{pc} (Fig. 1). For reversible and quasi-reversible ($\alpha = 0.5$) charge transfer without coupled chemical reactions, the following equation holds irrespective of the sweep rate

$$i_{\mathrm{pa}}/i_{\mathrm{pc}} = 1 \tag{7}$$

However, it is not quite so easy to determine the current base line in the reverse sweep. Various methods of evaluation have been proposed[18,55]. The most suitable, however, is an empirical formula derived by *Nicholson* [Eq. (8)], whose sole precondition is that the switching potential E_{λ} lies ca. 60 mV/n after the peak potential[56] (Fig. 1).

$$\frac{i_{\mathrm{pa}}}{i_{\mathrm{pc}}} = \frac{i_{\mathrm{ao}}}{i_{\mathrm{pc}}} + \frac{0.485\, i_{\lambda 0}}{i_{\mathrm{pc}}} + 0.086 \tag{8}$$

The evaluation of the separation of the peak potentials [Eq. (9)] is even more informative for the interpretation of pure E processes

$$\Delta E_{\mathrm{p}} = E_{\mathrm{pa}} - E_{\mathrm{pc}} \tag{9}$$

This permits the determination of the half-wave potential of the measured redox reactions, a concept borrowed from classical polarography [Eq. (10)].

$$E_{1/2} = E_{\mathrm{pa}} - \Delta E_{\mathrm{p}}/2 = (E_{\mathrm{pa}} + E_{\mathrm{pc}})/2 \tag{10}$$

$$0.3 \leqq \alpha \leqq 0.7;\ E_{\lambda} \leqq E_{\mathrm{pc}} - 100\ \mathrm{mV}$$

In terms of Eq. (11), $E_{1/2}$ is associated with the thermodynamic standard redox potential E^{0}

$$E_{1/2} = E^{0} + (RT/\mathrm{n}F)\ln(D_{\mathrm{R}}/D_{0})^{1/2} \tag{11}$$

As there is generally little difference between the diffusion coefficients of the oxidized and reduced forms, $E_{1/2}$ largely corresponds to the thermodynamic redox potential of the redox pair studied.

ΔE_{p} is also a measure for the reversibility of the charge transfer. Under Nernst conditions, i.e. for very fast charge transfer, ΔE_{p} is given by

$$\Delta E_{\mathrm{p}} = \frac{2.3\,RT}{\mathrm{n}F} = \frac{56.5}{\mathrm{n}}\ \mathrm{mV}\ (25\,^{\circ}\mathrm{C}) \tag{12}$$

ΔE_{p} increases as the heterogeneous standard rate of the charge transfer decreases and/or the sweep rate, which controls the experimental time-scale and can be varied over several orders of magnitude, is raised. The peak potential separation can be correlated unequivocally with the heterogeneous standard rate constant k^{0} of the electrode reactions to be analyzed using the kinetic parameter ψ, introduced by *Nicholson* [Eqs. (13) and (14)][57].

$$\psi = \frac{D_{0}^{\alpha/2}/D_{\mathrm{R}}^{\alpha/2}\cdot k^{0}}{\left(D_{0}\pi\dfrac{\mathrm{n}F}{RT}v\right)^{1/2}} \approx \frac{k^{0}}{\left(D_{0}\pi\dfrac{\mathrm{n}F}{RT}v\right)^{1/2}} \tag{13}$$

$$\Delta E_{\mathrm{p}} = \mathrm{f}(\psi) \tag{14}$$

It should be clear from Table 2[52,57] that for $\psi > 10$ the electrode reactions in the chosen time-scale are reversible. At the usual sweep rate of 100 mV/s, k^{0} values of up to 10^{-1} cm/s be derived from a cyclic voltammogram.

Besides the above-mentioned diagnostic criteria, there is a series of other significant characteristics of simple charge transfer. These are described in the literature[21,23]; most of them, however, have only special applications.

Table 2. Separation of the anodic and cathodic peak potentials as a function of the kinetic parameter ψ [Eqn. (13)] in the cyclic voltammogramm at $T = 25\,^{\circ}C$; position of the switching potential $|E_\lambda - E^0| = 150$ mV.

$\lvert\Delta E_p\rvert$ [mV]	ψ	$\lvert\Delta E_p\rvert$ [mV]	ψ
60	19.00	95	0.653
61	11.50	100	0.568
62	8.40	105	0.496
63	6.45	110	0.441
64	5.10	115	0.394
65	4.30	120	0.356
66	3.63	125	0.323
67	3.16	130	0.295
68	2.81	135	0.269
69	2.51	140	0.248
70	2.26	145	0.229
75	1.51	150	0.212
80	1.14	160	0.185
85	0.92	170	0.162
90	0.77		

3.2. Multielectron Transfer Processes

3.2.1. *The EE Mechanism*

The reduction of many inorganic ions such as Zn^{2+}, Pb^{2+} and Fe^{2+} is formally a "2e" transfer process. In fact, pure "2e" transfers in *one* elementary step are extremely unlikely because of the activation barrier. Multielectron transfer usually takes place in separate steps. For each heterogeneous electron transfer there is a rate relationship, as expressed by Eq. (2), characterized by the heterogeneous rate constant as well as the standard potential. Depending on the separation between the theoretical potentials of the redox reactions, several cases have to be distinguished. Again, in the interests of simplicity only a reduction is discussed here.

$$Ox \overset{E_1^0}{\rightleftharpoons} Red_1 \tag{15a}$$

$$Red_1 \overset{E_2^0}{\rightleftharpoons} Red_2 \tag{15b}$$

Case 1: $E_1^0 > E_2^0$

If the separation of the potentials between the redox transfers is large ($\Delta E^0 > 150$ mV), the resulting cyclic voltammogram consists of two typical, additively superimposed, one-electron transfer waves (Fig. 6). However, the electrode process as a whole is more complicated than appears at first sight. At the same time as the heterogeneous electron-transfer at the electrode interface, fast homogeneous electron-transfer reactions also occur, which, in multielectron transfer systems, lead to disproportionation or comproportionation. Hence, every EE mechanism can in principle be treated as an E_{disp} mechanism[59].

$$2\,Red_1 \underset{k_b}{\overset{k_f}{\rightleftharpoons}} Ox + Red_2 \tag{16}$$

The equilibrium position for the disproportionation is usually reached within the time scale of voltammetric measurements. The disproportionation constant

$$K = [Ox][Red_2]/[Red_1]^2 \tag{17}$$

can be derived from the difference between the standard potentials using Eq. (18).

$$-RT\ln K = nF(E_1^0 - E_2^0) \tag{18}$$

In recent years improvements in sample preparation techniques[46,48,49] and the use of unconventional solvent/electrolyte systems such as SO_2/tetra-*n*-butylammonium perchlorate (TBAP) or NH_3/KI[60,61] have made it considerably simpler to determine standard potentials and disproportionation constants. It has thus become possible to generate electrochemically stable dianions and dications[60-64] from pure aromatics as well as from their substituted derivatives. In addition, the use of ultramicroelectrodes together with extremely high sweep rates (v = 10000 V/s) has facilitated the measurement of redox potentials of very reactive systems[65]. The disproportionation which occurs simultaneously with the electrode reactions in solution causes the concentration profiles of the redox couples to adapt to the equilibrium during diffusion. However, as long as Nernst conditions hold at the electrode, the dispro-

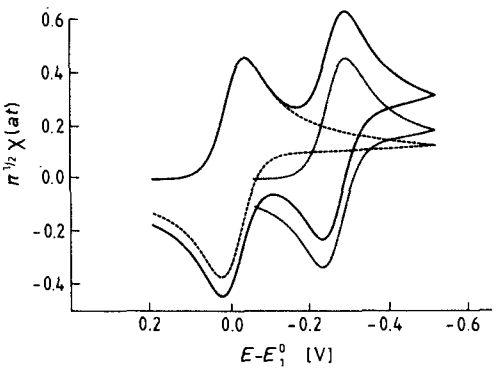


Fig. 6. Cyclic voltammogram for the EE mechanism: (——) 1e⁻ transfer at $E_1^0 = 0.0$ V *and* at $E_2^0 = -0.25$ V; (----) 1e⁻ transfer at E_1^0, (· · · ·) 1e⁻ transfer at E_2^0.

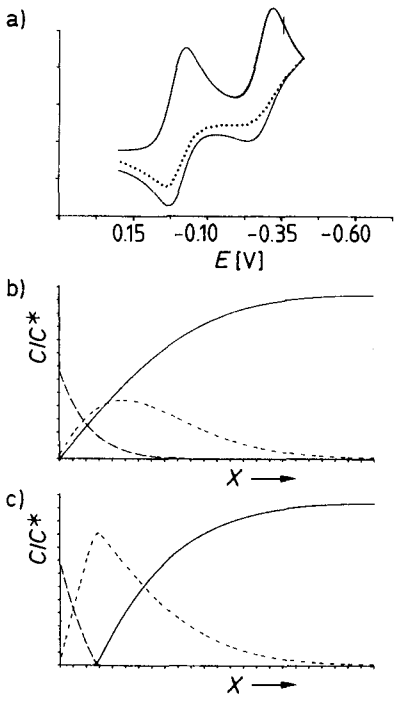


Fig. 7. a) Cyclic voltammograms for the EEC mechanism, $k_f/a = 0.5$, k_f = homogeneous rate constant of the follow-up reaction, a = sweep rate; (——) with disproportionation, (· · ·) without disproportionation; concentration profiles at $E = -0.35$ V; b) without disproportionation; and c) with disproportionation; (——) A, (– – –) $A^{\ominus}$, (— — —) $A^{2\ominus}$.

portionation is not directly visible in the cyclic voltammogram[62]. Significant changes occur only with quasi- or irreversible charge transfer or with subsequent chemical follow-up reactions (Fig. 7), and these must be taken into account in interpretating experimental data.

Case 2: $E_1^0 = E_2^0$

If the difference between the standard potentials of the two redox reactions is less than 100 mV, only a single wave appears in the voltammogram. When $\Delta E^0 = 0$, ΔE_p drops to 42 mV and the current function has a value 2.41 times that of a one-electron transfer (Fig. 8). The situation where structurally identical redox centers in one molecule do not interact constitutes a special case. Under these conditions electron transfers to the two centers are purely statistical[66,67]. The formal separation in standard potentials is then

$$\Delta E^0 = -\frac{RT}{F} \ln 4 = -35.7 \text{ mV } (25\,^\circ\text{C}) \qquad (19)$$

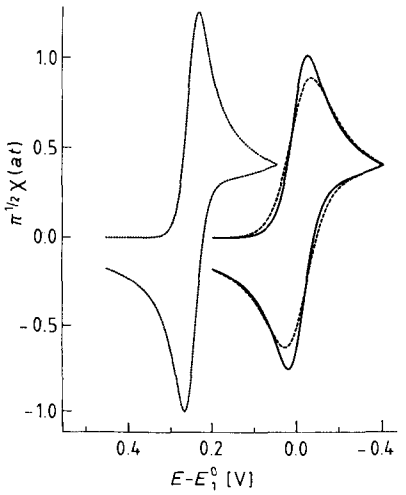


Fig. 8. Cyclic voltammograms for EE mechanisms with different E_1^0, E_2^0 potentials: (—) $E_1^0 = E_2^0 = 0.0$ V, $\Delta E_p = 42$ mV; (----) $E_1^0 = 0.0$ V, $E_2^0 = -0.035$ V, $\Delta E_p = 58$ mV; (····) $E_1^0 = 0.0$ V, $E_2^0 = 0.500$ V, $\Delta E_p = 29$ mV.

The resulting voltammograms (Fig. 8) are consistent with the normal E mechanism with $\Delta E_p = 58$ mV, but the current is twice as high. Two-step redox systems of this nature are usually present when the redox centers are separated from one another by either a fairly long polyene chain ($n \geq 4-5$) or an alkane chain ($n \geq 3$) or are in the *meta*-position in an arene[68]. *Hünig* et al. have studied numerous examples, but have not theoretically analyzed the cyclic voltammograms[69].

Case 3: $E_1^0 < E_2^0$

The energy required for the second electron transfer is less than for the first. In the ideal case ($\Delta E^0 < -180$ mV) such redox processes can be identified thus: in the cyclic voltammogram the ΔE_p splitting drops to 28.5 mV (25 °C) and the measurable current rises to a value equal to 2.82 times ($= 2^{3/2}$) that of a corresponding 1e-transfer. In contrast, it is not easy to determine the individual standard potentials, as the formal measurable half-wave potential

$$E_{1/2} = (E_1^0 + E_2^0)/2 \qquad (20)$$

corresponds to the mean value of both standard potentials.

Numerous examples of these "classical" 2e reactions, especially from inorganic and organometallic chemistry, have been discussed in the literature[70,71]. However, the diagnostic pattern for characterizing such processes can be applied only to fast heterogeneous charge-transfer reactions[62]. The picture for analogous 2e reactions of organic compounds is often quite different, as illustrated, for example, by slow heterogeneous reactions. The best-known example of this is cyclooctotetraene, for which in NH_3/KI the potential for the second, fast reaction step is 160 mV more positive than that for the kinetically slower first step[72]. Under these conditions quantitative analysis is possible only by numerical computation of the whole current-voltage curve (cf. Section 6).

3.2.2. *EEEE... Mechanisms*

Previously, more than two reversible charge-transfer steps were seldom observed in monomeric systems. Examples are mostly restricted to organotransition-metal compounds[1,73]. However, improvements in experimental techniques (cf. Section 2) have facilitated the reduction of highly reactive arenes possessing appropriate structural properties—e.g. 9,9′-bianthryl (Fig. 21) and its homologues or decacyclene **1**—to tetraanions or even hexaanions (Fig. 9)[74–76]. It is possible to completely evaluate the voltammogram provided the waves are clearly separated and the reactions are reversible. Otherwise one has to revert to digital simulation.

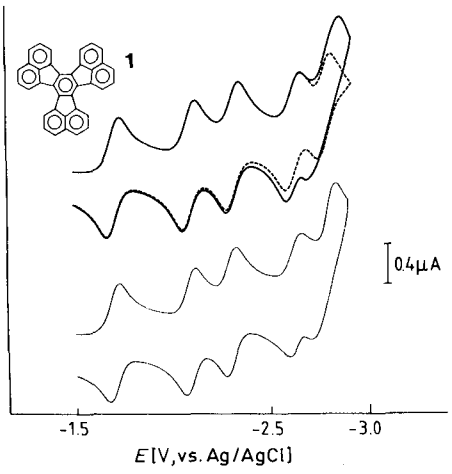


Fig. 9. Experimental (bottom) and simulated (top) cyclic voltammograms for **1** at −10 °C in tetrahydrofuran (THF)/$NaBPh_4$; (----) simulation with five redox steps, (——) simulation with six redox steps; $\vartheta = 50$ mV/s.

The majority of multicharge transfer reactions occur in polymers. These comprise, on the one hand, redox polymers, including biopolymers[77] with largely isolated cen-

ters and low intramolecular interaction and, on the other hand, conducting polymers whose charged redox centers interact strongly[78].

Evaluations are complicated by the fact that polymers are often insoluble or, if soluble, are quickly adsorbed at the electrode surface. Provided there are no interactions between chemically identical centers, theory predicts for an n-fold charge transfer voltammograms whose form corresponds to the $1e^-$ transfer case, but whose current values have the n-fold value of the $1e^-$ transfer[67]. For chemically non-equivalent, weakly interacting redox centers, as observed, e.g. in enzymes such as cytochrome, the cyclic voltammograms have to be analyzed by computer simulation[79] (cf. Section 6).

The cyclic voltammograms of insoluble redox polymers formally resemble those obtained in thin-layer cells[54] with a high surface/volume ratio; however, they are more consistent with models which describe the properties of totally adsorbed redox systems[80]. In the meantime, several research groups have developed other model concepts which discuss, inter alia, electron hopping mechanisms and the diffusion of the electrolyte counterion as rate determining steps[81–83]. Cyclic voltammograms are also being increasingly used to analyze the electrochemical properties of conducting polymers[84], graphite, and intercalated compounds[85]. However, interpretations are primarily phenomenological, concerning, for instance, the reversible charging and discharging of such systems as a function of potential and solution parameters (Fig. 10).

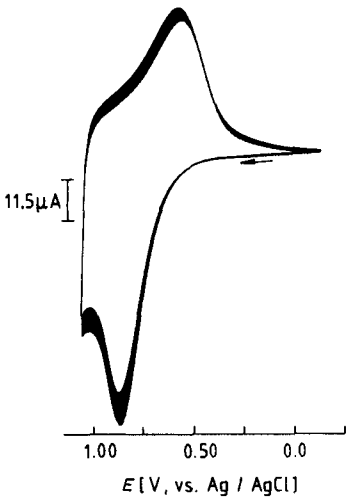


Fig. 10. Experimental cyclic voltammogram for the reversible oxidation (increasing current characteristics!) of polyacetylene in propionitrile/[TBA]PF_6. The CV was measured using a polymer-coated Pt electrode, $v = 200$ mV/s.

4. Electron Transfer with Coupled Chemical Reactions

Although charge-transfer processes are an important part of the entire spectrum of chemical reactions, they seldom occur as isolated elementary steps. In contrast, electron-transfer reactions coupled with bonding or bond-breaking steps are very frequent. Cyclic voltammetric experiments show the stability of both the educt and the product of the charge transfer. Accordingly, the method is suitable for both qualitative and quantitative characterization of chemical reactions which either precede or follow the charge transfer[21,23,86–91]. Scheme 1 lists the most important mechanisms for which cyclic voltammograms have been analyzed theoretically. A few examples are discussed in the following sections.

E	$A \overset{e}{\rightleftharpoons} B$	[11–16, 57]
EE_{disp}	$A \overset{e}{\rightleftharpoons} B$ $B \overset{e}{\rightleftharpoons} C$ $2B \overset{K_d}{\rightleftharpoons} A + C$	[18, 62, 66, 171]
EEEE...	$A \overset{e}{\rightleftharpoons} B \overset{e}{\rightleftharpoons} C \ldots$	[67, 171, 177]
$C_{1rev}E$	$A \underset{k_b}{\overset{k_f}{\rightleftharpoons}} B \overset{e}{\rightleftharpoons} C$	[16, 153]
$C_{1rev}EE$	$A \underset{k_b}{\overset{k_f}{\rightleftharpoons}} B \overset{e}{\rightleftharpoons} C$ (e)	[160, 155]
$EC_{1rev,irr}$	$A \overset{e}{\rightleftharpoons} B$ $B \underset{k_b}{\overset{k_f}{\rightleftharpoons}} C$	[16, 56, 101, 177]
$EC_{2rev,irr}$	$A \overset{e}{\rightleftharpoons} B$ $2B \underset{k_b}{\overset{k_f}{\rightleftharpoons}} C$	[96–101, 115]
$EC_{2rev,irr}$	..... $B + A \underset{k_b}{\overset{k_f}{\rightleftharpoons}} C$	[97]
$EC_{2rev,irr}$	..... $B + Z \xrightarrow{k_f} C$	[101]
EC_{nrev}	..... $nB \underset{k_b}{\overset{k_f}{\rightleftharpoons}} qC$	[99]
EC_{cat}	$A \overset{e}{\rightleftharpoons} B$ $B + Z$	[16]
ECE_{disp}	$A \overset{e}{\rightleftharpoons} B$ $B \overset{k}{\rightleftharpoons} C$ $C \overset{e}{\rightleftharpoons} D$ $B + C \overset{K_d}{\rightleftharpoons} A + D$	[17, 101, 124–127, 97]
$\bar{E}C\bar{E}_{disp}$	$A \overset{+e}{\rightleftharpoons} B^{\ominus}$ $B^{\ominus} \overset{k}{\rightleftharpoons} C^{\ominus}$ $C^{\ominus} \overset{-e}{\rightleftharpoons} D$ $C^{\ominus} + A \overset{K_d}{\rightleftharpoons} D + B^{\ominus}$	[143, 147, 151]

Scheme 1. List of the most important electrochemical mechanisms whose cyclic voltammograms have been theoretically analyzed.

4.1. EC Mechanisms

The simplest mechanism is electron transfer with a subsequent first-order, irreversible chemical follow-up reaction (EC_{irr}).

$$A \overset{e}{\rightleftharpoons} A^{\ominus} \tag{21}$$

$$A^{\ominus} \xrightarrow{k_f} B \tag{22}$$

In the follow-up reaction the initially formed anion $A^{\ominus}$ decays and a new species **B** is formed (Fig. 11). In consequence, only a small amount of the primary anion is avail-

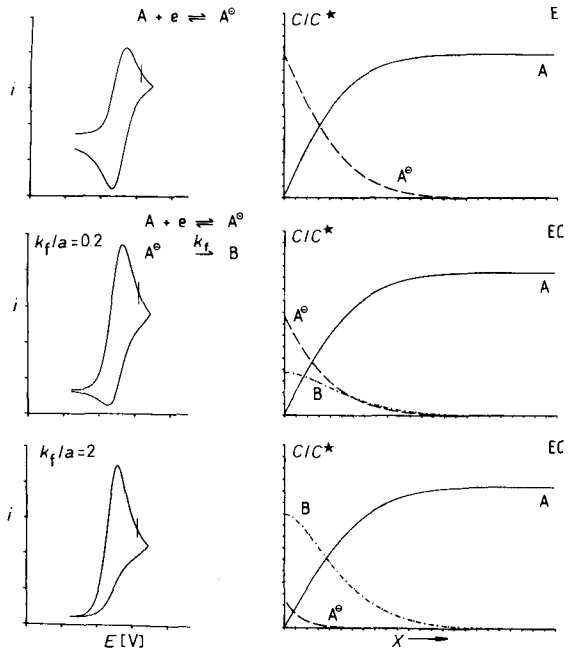


Fig. 11. Cyclic voltammograms (left) and accompanying concentration profiles for a coupled chemical, first-order, irreversible, follow-up reaction; k_f/a = dimensionless rate constant, | potential value at which concentration profiles were calculated.

able for oxidation in the reverse sweep, depending on the rate of the follow-up reaction and the sweep rate. Accordingly, the corresponding anodic current in the cyclic voltammogram decreases until it disappears at high rate constants and low sweep rates. The rate constant of the follow-up reaction can be determined from the ratio of the anodic and cathodic peak currents of the cyclic voltammetric curve at an appropriate sweep rate. The current ratio and the homogeneous kinetic parameters are correlated using theoretical working curves in which — to save computer time and effort — the kinetic parameters are dimensionless[18]. Because of this simplification, experimental data from different measurements can be evaluated with just a few working curves (Fig. 12). Thus, the dimensionless kinetic parameter for a first-order reaction is $k_{f_1} \cdot \tau$ (τ = time

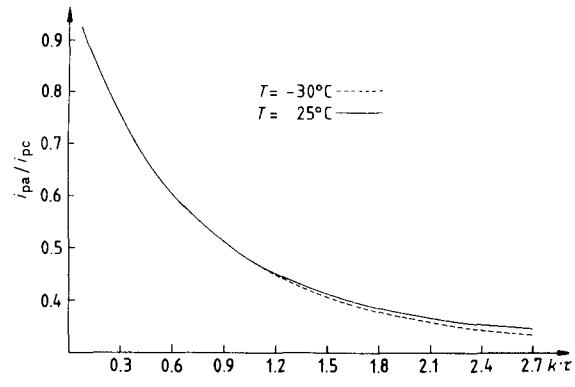


Fig. 12. Working curves for a coupled first-order (irreversible), follow-up reaction (EC_{irr}), τ: time elapsed between passing the E^0 potential and reaching the switching potential E_λ; k [s^{-1}] = homogeneous rate constant of the follow-up reaction.

between passing the E° potential and reaching the switching potential E_λ) and for a second-order reaction, $k_{f_2} \cdot c^* / a$.

In addition to the current ratio, other (diagnostic) criteria also indicate a coupled chemical reaction, e.g. a shift in the peak potential as a function of the kinetic parameters. Details are provided in the literature[21,23,86]. However, they can be used to quantitatively interpret electrochemical reaction mechanisms only if characteristic reference parameters of the undisturbed charge transfer are available, e.g. E°, or if, as in the case of second-order reactions, the peak potential shift can be measured as a function of the substrate concentration. As a general rule, for reduction processes the peak potential values shift in the anodic direction as the rate constants of the subsequent reactions increase. Hence, they do not correspond to thermodynamic redox potentials.

Although the coupled irreversible first-order, chemical follow-reactions form an elementary step in many electrochemical processes, only in a few favorable cases can the "pure" EC mechanism be recognized in the cyclic voltammogram. A further prerequisite for a successful kinetic analysis using cyclic voltammograms is that the intermediate should have a life-time $\geq 10^{-4}$ s. The reason for this is technical, since at scan rates above 1000 V/s the capacitive currents, which are directly proportional to v, gradually overlap with the Faradaic part of the current. In principle, the rate constants of the follow-up reaction can also be derived from irreversible waves provided the half-wave potential of the reversible electrode reaction is known.

Slow first-order EC reactions have been observed and analyzed in the following cases: electron-transfer induced valence isomerizations[92] and conformational changes[93], as well as the reduction of aryl halides[94,95].

Second-order EC reactions are far more common. Several variants are possible: reactions of the electron-transfer product with itself[96–100], with the educt[97], or with another compound present in the solution[101]. In addition, one must distinguish between reversible and irreversible processes. Second-order follow-up reactions can usually be recognized by the concentration dependence of corresponding cyclic voltammograms: with decreasing substrate concentrations, reversible currentvoltage curves are observed even at low sweep rates. The quantitative evaluation can be made with the aid of either calculated working curves[98,102] or by digital simulation[103].

The mechanistic analysis of such processes became relevant as a result of the technologically important reductive dimerization of activated olefins[104–108], as performed industrially in the electrosynthesis of adipodinitrile from acrylonitrile. Studies conducted with different electroanalytical methods show that for the most part radical-radical dimerization dominates over radical-educt coupling. Apart from the coupling reactions of neutral phenoxyl[109,110] and pyranyl radicals[111] or of inorganic radical ions such as SO_2[112], cyclic voltammetry has recently also been used to investigate and, in part, quantitatively evaluate the dimerizations of aromatic radical anions[113–115].

The radical-radical coupling of the anion of 9-anthracenecarbonitrile **2** is one of the most interesting examples of reversible chemical dimerization [Eq. (23)].

$$\mathrm{A} \overset{e}{\rightleftharpoons} \mathrm{A}^{\ominus}$$
$$2\,\mathrm{A}^{\ominus} \underset{k_b}{\overset{k_f}{\rightleftharpoons}} \mathrm{A}_2^{2\ominus} \qquad (23)$$

Contrary to expectations, this gives at low sweep rates a cyclic voltammogram whose wave-form is reversible and whose anodic current peak gradually disappears as v (V/s) increases (Fig. 13)[103,113-115]. The explanation of this phenomenon is that at low scan rates the chemical reaction is in thermodynamic equilibrium. The cyclic voltammogram is shifted anodically as the value of the equilibrium constant increases but retains its characteristic reversible form[96]. As v increases the system falls under kinetic control, i.e. on this time scale chiefly the dimer is produced at the cost of the slow reverse reaction. The cyclic voltammogram becomes irreversible. If the time scale is short enough, the kinetics of dimerization remain incomplete, and the (true) reversible state is approached. By using the dimensionless kinetic paramter ψ, which takes into account the substrate concentration c^*, the equilibrium constant K, the rate constants k_f [L mol^{-1} s^{-1}] and k_b [s^{-1}] of the forward and reverse reactions as well as the scan rate, the limiting cases of this EC_{2rev} mechanism can be formulated [Eq. (24)]

$$\psi = \frac{Kc^*}{[(k_f c^* + k_b c^*)/a]^{1/2}} = \frac{Kc^*}{(lc^*/a)^{1/2}} \qquad (24)$$

where $l = k_f + k_b$

1. k_f and $k_b \to \infty$ or $a \to 0$: system in dynamic dimerization equilibrium, reversible *potential-shifted* cyclic voltammograms;
2. k_f and $k_b \to 0$ or $a \to \infty$: no follow-up reaction, pure charge-transfer process;
3. $l/a \to \infty$ and $\psi \to \infty$, $k_f \gg k_b$, $K \gg 1$: irreversible follow-up chemical reaction.

The quantitative evaluation of the voltammograms of **2** (propionitrile, 20 °C) using digital simulation methods (cf. Section 6) gives a value of 2×10^4 L·mol^{-1}·s^{-1} for the dimerization rate constant k_f and 3.5 s^{-1} for k_b. Accordingly, the thermodynamic equilibrium constant $K = 5.7 \times 10^3$ L·mol^{-1} [103].

In contrast to the dimerizations of radical anions, the radical-substrate coupling seems to be an important reaction

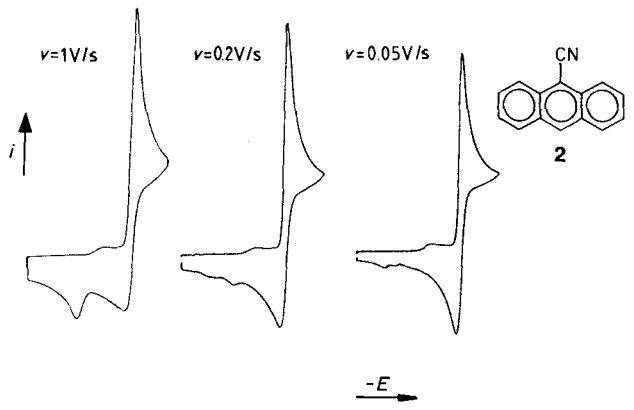


Fig. 13. Cyclic voltammograms for the reduction of **2** in propionitrile/[TBA]PF_6 at different scan rates.

path for radical cations[116-118]. This is due to the quantum mechanical exchange interactions between the cation and the neutral species[119], which facilitate formation of a charge-transfer bond.

Important examples of radical-substrate dimerization have been shown to occur in the electrocrystallization of radical cations of aromatic compounds[26].

Due to their high conductivity, crystalline radical cation salts are "organic metals", and for this reason are studied intensively by solid-state physicists[120]. X-ray structure analysis has shown that, besides the ideal composition $A_2^{\oplus}X^{\ominus}$, as observed in the electrocrystallization of fluoroanthene **3** ($X = PF_6$), different stoichiometries occur in many systems depending on the reaction conditions (solvent, temperature, concentration)[121,122]. The type and kinetics of coupled chemical reactions, whose products in solution determine the stoichiometry of the crystals, were clarified for some exemplary systems with the aid of cyclic voltammetric measurements in conjunction with digital simulation (Scheme 2)[123].

$$\begin{aligned}
&\mathrm{A} && \overset{E_1}{\rightleftharpoons} \mathrm{A}^{\odot\oplus} + \mathrm{e}\\
&\mathrm{A}^{\odot\oplus} + \mathrm{A} && \overset{K_1}{\rightleftharpoons} [\mathrm{A}_2]^{\odot\oplus}_{\mathrm{compl.}}\\
&[\mathrm{A}_2]_{\mathrm{compl.}} && \overset{E_2}{\rightleftharpoons} [\mathrm{A}_2]^{2\oplus}_{\mathrm{compl.}} + \mathrm{e}\\
&\mathrm{A}^{\odot\oplus} + \mathrm{A}^{\odot\oplus} && \overset{K_{II}}{\rightleftharpoons} [\mathrm{A}_2]^{2\oplus}_{\mathrm{compl.}}\\
&[\mathrm{A}_2]^{\odot\oplus}_{\mathrm{compl.}} + \mathrm{A}^{\odot\oplus} && \overset{K_{\mathrm{disp}}}{\rightleftharpoons} [\mathrm{A}_2]^{2\oplus}_{\mathrm{compl.}} + \mathrm{A}\\
&\mathrm{A}^{\odot\oplus} + \mathrm{R} && \longrightarrow \mathrm{A}\,\mathrm{R}^{\odot\oplus}\\
&[\mathrm{A}_2]^{n\oplus}_{\mathrm{compl.}} + n\mathrm{X}^{\ominus} && \rightleftharpoons \{[\mathrm{A}_2]^{n\oplus}(\mathrm{X}^{\ominus})_n\}_{\mathrm{ads.}}\\
&\{[\mathrm{A}_2]^{n\oplus}(\mathrm{X}^{\ominus})_n\}_{\mathrm{ads.}} && \longrightarrow \{[\mathrm{A}_2]^{n\oplus}(\mathrm{X}^{\ominus})_n\}_{\mathrm{cryst.}}
\end{aligned}$$

Scheme 2. Reaction steps in the electrocrystallization of salts with radical cations; the indices compl. and ads. indicate complexation and adsorption at the metal electrode, respectively.

The radical cations $A^{\odot\oplus}$ produced at the electrode form dimeric monocations $A_2^{\odot\oplus}$ with the substrate present in solution in an equilibrium reaction. At a slightly more positive potential these are oxidized to the much more unstable dimeric dications $A_2^{2\oplus}$, which are simultaneously also products of a direct radical-radical dimerization. The stability of the dimeric monocations $A_2^{\odot\oplus}$ is apparent from the voltammograms. For **3** these show a high formation constant — the amount of oxidizable $A_2^{\odot\oplus}$ is large, but pyrene **4**, in contrast, has a much smaller constant and the oxidizable amount of $A_2^{\odot\oplus}$ is small (Fig. 14). For **4** ($X = PF_6$, AsF_6, ClO_4) the stoichiometry of the crystals is influenced by the high proportion of monomeric cations as well as by unreacted substrate, whereas **3** ($X = PF_6$, AsF_6, ClO_4) contains almost exclusively crystalline material of composition $A_2^{\oplus}X^{\ominus}$.

4.2. ECE Mechanism

The two-step mechanisms with coupled chemical reaction described in the previous section are, as the last example has shown, often part processes in a complicated reaction. In most cases the product of a subsequent reaction is itself once again electroactive. The result is the well-known ECE mechanism, in which the chemical reaction can be of either the first[17,101,124-127] or second[97] order.

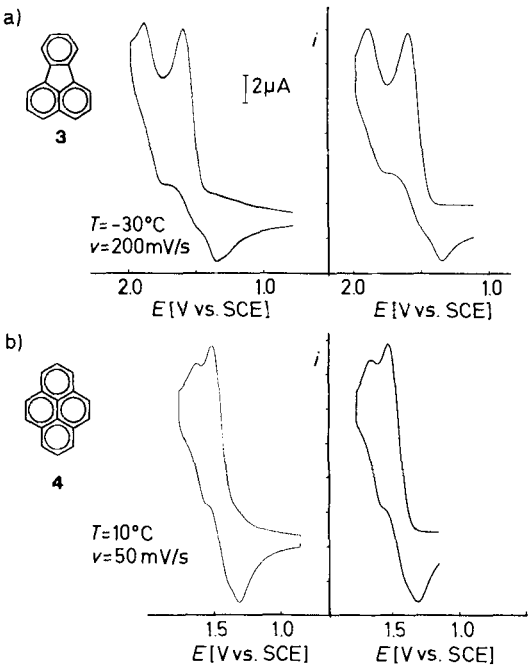


Fig. 14. a) Experimental (left) and simulated (right) cyclic voltammograms for the oxidation of a) **3** and b) **4** in CH_2Cl_2.

$$\mathbf{A} \overset{E_1^0}{\rightleftharpoons} \mathbf{B} \tag{25}$$

$$\mathbf{B} \overset{k_f}{\rightleftharpoons} \mathbf{C} \tag{26}$$

$$\mathbf{C} \overset{E_2^0}{\rightleftharpoons} \mathbf{D} \tag{27}$$

$$\mathbf{B} + \mathbf{C} \overset{K_D}{\rightleftharpoons} \mathbf{A} + \mathbf{D} \tag{28}$$

Depending on the separation of the standard potentials of the two redox couples, one must distinguish between three situations (Fig. 15). Provided that the potential of the second redox step is much lower than that of the first (i.e., $E_1^0 > E_2^0$ for reduction), the homogeneous kinetic parameters can be determined without difficulty from the CV data of the first redox wave by analogy to a normal EC reaction. In other words by using appropriate sweep rates and switching potentials E_λ the rate constants can be deduced from the current ratio i_{pa}/i_{pc} with the help of suitable

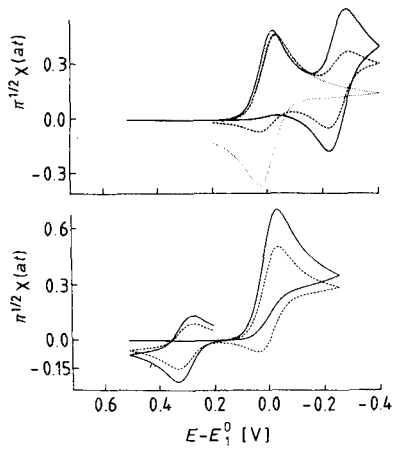


Fig. 15. Simulated cyclic voltammograms of the ECE mechanism with homogeneous disproportionation; (····) $k_f/a = 0.0$, (---) $k_f/a = 0.1$, (—) $k_f/a = 1.0$; above: $E_1^0 = 0.0$, $E_2^0 = -0.25$ V; below: $E_1^0 = 0.0$, $E_2^0 = 0.3$ V.

working curves. The second wave can also be used to analyze the kinetics of the follow-up reaction, in which the peak current is an unequivocal function of the ΔE^0 separation, the sweep rate, and the homogeneous rate constant.

For equal standard potentials ($E_1^0 = E_2^0$), one observes as a rule a single apparently reversible wave whose current ratio, however, is always less than 1 and, for large rate constants, can drop as low as 0.5.

If $E_1^0 < E_2^0$, the CV has an irreversible step in the first cycle at ca. E_1^0; the value of its current amplitude in fast follow-up reactions is *twice* that of a one-electron transfer reaction[128] (Fig. 15). The increase in the current amplitude arises because the second electron transfer, although thermodynamically favored, can occur only after the first electron transfer and formation of the follow-up product **C**. Accordingly, reoxidation of the **C/D** redox pair only becomes visible at ca. E_2^0 in the anodic part of the voltammogram after the E_1^0 potential has again been passed. The irreversibility of the E_1^0 wave, a consequence of the chemical follow-up reaction, corresponds to the amplitude of the current in the second redox step.

The obvious comparison between the ECE mechanism and the EE reaction (cf. Section 3.2.1.) shows that both electron-transfer steps are coupled in a similar way to one another via a homogeneous disproportionation[124–127]. Hence, the product **D** is not only formed by heterogeneous electron-transfer but, in accordance with Eq. (28) (for reduction reactions where $E_2^0 \geqslant E_1^0$), also by homogeneous electron-transfers in a competing reaction. The influence of the disproportionation on the shape of the cyclic voltammogram is complicated and can cause considerable difficulties in its evaluation. Hence, the quantitative analysis of ECE mechanisms requires digital simulations and a direct comparison between the experimental and calculated cyclic voltammograms.

For a long time there was little experimental data on ECE mechanisms. The standard example described in the literature was usually the reduction of nitrosophenols[129, 130]. Only since the late 1960s has it become obvious, especially through the experimental research of *Adams, Nelson* et al.[22, 131–133] and *Parker* et al.[134, 135], that the ECE mechanism, including the homogeneous disproportionation, embodied an important mechanistic principle in electrochemical reactions. It is now almost impossible to keep up with all new work in the field. The ECE mechanism occurs in virtually all chemical reactions induced by electron transfer, including, inter alia, isomerizations, couplings, substitutions, additions, and eliminations[89, 136–139]. In most of these reactions the second e-transfer is energetically more favorable than the first, so that the appearence of a single irreversible wave with *twice* the current amplitude of the 1e norm in the forward sweep of the cyclic voltammogram is a hallmark of the ECE reaction (Fig. 15). However, improved experimental and theoretical methods of monitoring and evaluating cyclic voltammograms verify that the simple ECE scheme is often disturbed by competing parallel reactions or further follow-up reactions[88, 140–142].

The efficiency of cyclic voltammetric measurements in characterizing elementary steps and determining kinetic parameters of electron-transfer induced reactions is im-

pressively illustrated by one variant of the ECE mechanism. This development was initiated by *Feldberg* et al.[143]. In this case, after the chemical follow-up product has been formed the second electron transfer occurs, in contrast to the normal case, in the *reverse* direction to the E_1^0 step.

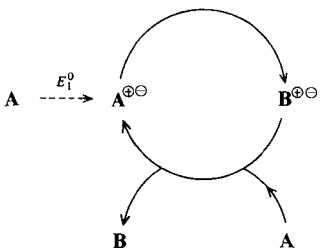
$$\mathbf{A} \mp e \rightleftharpoons \mathbf{A}^{\oplus\ominus}[*] \quad (29)$$

$$\mathbf{A}^{\oplus\ominus} \xrightarrow{k} \mathbf{B}^{\oplus\ominus} \quad (30)$$

$$\mathbf{B}^{\oplus\ominus} \pm e \rightleftharpoons \mathbf{B} \quad (31)$$

$$\mathbf{B}^{\oplus\ominus} + \mathbf{A} \rightleftharpoons \mathbf{B} + \mathbf{A}^{\oplus\ominus} \quad (32)$$

The ion **A** formed at the potential E_1^0 is transformed in one (or more) chemical steps into the species $\mathbf{B}^{\oplus\ominus}$, which, provided $|E_2^0| > |E_1^0|$, in turn spontaneously changes into the product **B**. The electron transfer from $\mathbf{B}^{\oplus\ominus}$ to **B** can occur both heterogeneously at the electrode [Eq. (31)] or homogeneously in solution [Eq. (32)]. The homogeneous electron transfer is of crucial importance, since by this means the chemically unstable species $\mathbf{A}^{\oplus\ominus}$ is permanently reproduced [Eq. (32)]. A chain reaction takes place which, under favorable conditions — i.e. no terminating reactions — is catalyzed by a single electron transfer from **A** to $\mathbf{A}^{\oplus\ominus}$; **A** is transformed quantitatively into **B** (Scheme 3).



Scheme 3.

Such ETC processes (*e*lectron *t*ransfer *c*hain) can be recognized in cyclic voltammograms since with small sweep rates and large values for the dimensionless kinetic parameter k_f/a the wave of the redox pair $\mathbf{A}/\mathbf{A}^{\oplus\ominus}$ disappears virtually completely (Fig. 16). The chain reaction induced by electron transfer ($\Delta G^\circ < 0$!) does not require any current. If the sweep rate is incremented the chemical reactions leading from $\mathbf{A}^{\oplus\ominus}$ to $\mathbf{B}^{\oplus\ominus}$ cannot be completed on the time scale of the experiment, with the result that in the cyclic voltammogram the redox wave of $\mathbf{A}/\mathbf{A}^{\oplus\ominus}$ increases, while the corresponding $\mathbf{B}/\mathbf{B}^{\oplus\ominus}$ wave disappears.

Initially the ETC concept was largely disregarded, but since the discovery by *Russell* et al. and *Bunnett*[144,145] of radical-nucleophilic aromatic substitution, the $S_{RN}1$ reaction, it has acquired great significance. Aryl halides ArX react with electron-rich nucleophiles (e.g. thiophenolate or diethylphosphite ions) via the radical anion intermediate $ArX^{\odot\ominus}$ to the corresponding substituted products. *Savéant* et al. have shown that the $S_{RN}1$ reaction can also be electrochemically triggered and, moreover, accurately analyzed by cyclic voltammetry[9,146,147]. Other ĒCĒ processes, which occur via rapid chain reactions include, e.g., the *cis-trans* isomerization of enol ethers[148], the transformation of epoxides into ketones[149], or the ligand substitution reactions of carbonylmetal complexes[150]. *Kochi* et al.[151] describe a particularly impressive example which is proved by cyclic voltammograms and digital simulation, namely ligand substitution reactions with carbonylmanganese complexes. Recently, cycloadditions have also been discussed in terms of ETC mechanisms[152]. Cyclic voltammetry could possible supply proof for this mechanistic hypothesis.

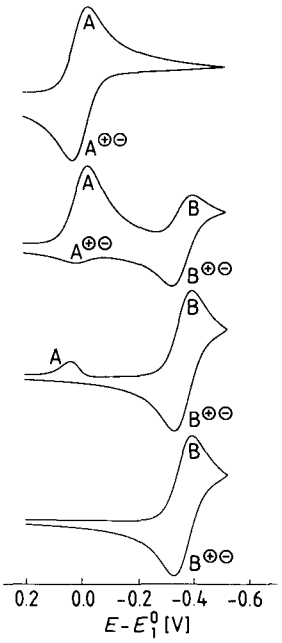


Fig. 16. Simulated cyclic voltammograms for the catalytic ĒCĒ mechanism; $E_1^0 = 0.0$ V, $E_2^0 = -0.35$ V; from top to bottom: $k_f/a = 0.0, 0.1, 10, \geq 100$.

4.3. The ECCEE Mechanism

The mechanisms analyzed in the previous sections constitute a small but experimentally significant part of the spectrum of elementary electrochemical reactions. Omissions include, e.g., CE mechanisms; although their theory has been studied in depth[116,153], only a few examples have been confirmed by voltammetric measurements[154,155]. Notwithstanding this, the number of different reaction channels is exceptionally large, and the interpretation of any one cyclic voltammogram should not follow standard schemes alone. An instructive example of this is the reduction of 10-fluoro-9-anthracenecarbonitrile **5**; at the same time it is a demonstration of the power of digital simulation[156].

As a rule, halogenated arenes are reduced electrochemically to the corresponding hydrocarbons by eliminating halides (ECEC reaction)[157]. Therefore, if one starts with **5** the expected final product of the electrode reaction is 9-anthracenecarbonitrile **2**. Cyclic voltammograms recorded at 0.5 V/s support this assumption in that the value of the peak current ratio of the first wave is less than 1 and in the reduction range of **2** the expected smaller, reversible wave appears. The only unusual aspect is the peak potential separation ΔE_p of ca. 200 mV in the first reduction wave (Fig.

[*] $\mathbf{A}^{\oplus\ominus}$ symbolizes both the cation $\mathbf{A}^{\oplus}$ and the anion $\mathbf{A}^{\ominus}$.

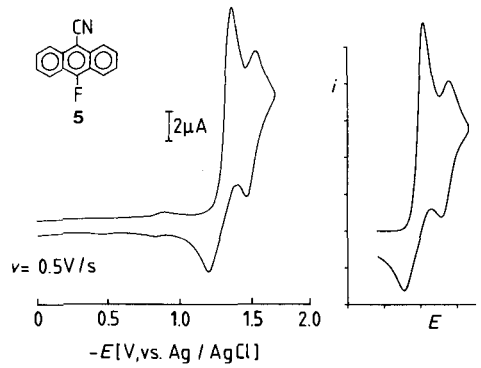
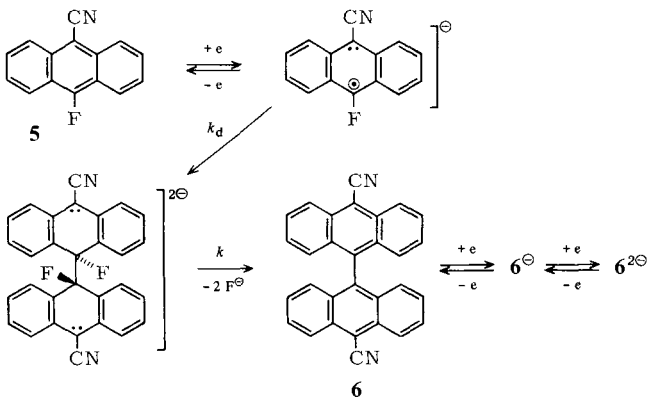


Fig. 17. Experimental (left) (propionitrile, [TBA]PF_6, 20°C) and simulated cyclic voltammograms for the reduction of **5** at 0.5 V/s.

17). But as soon as the sweep rate is increased to 10 V/s the misinterpretation becomes apparent: in the anodic part of the first wave a second peak appears (Fig. 18). As the sweep rate is increased the first anodic wave grows smaller; above 50 V/s the cyclic voltammogram approaches that of the reversible reduction of **5**. Both digital simulation of the voltammograms (Figs. 17, 18) and the results of the



product analysis — 10,10'-bi-9-anthracenecarbonitrile **6** is formed — reveal that the radical anion of **5** does not react further by eliminating fluoride but, by analogy to **2**, dimerizes to the dianion. A further one or two chemical steps follow in which the fluoride ions are eliminated and **6** is formed. The rate-determining step for the whole reaction is the dimerization, for which a rate constant $k_f = 1.2 \times 10^3$ L mol^{-1} s^{-1} was determined by computer simulation (20°C).

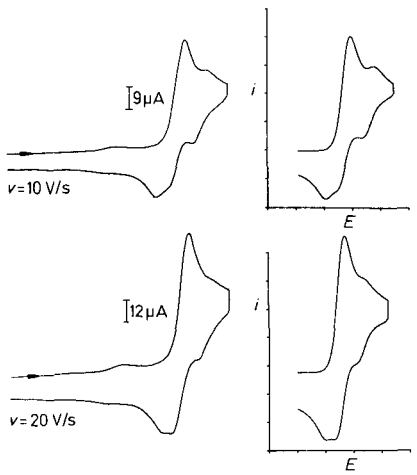


Fig. 18. Experimental (propionitrile, [TBA]PF_6, 20°C) and simulated cyclic voltammograms for the reduction of **5** at 10 and 20 V/s.

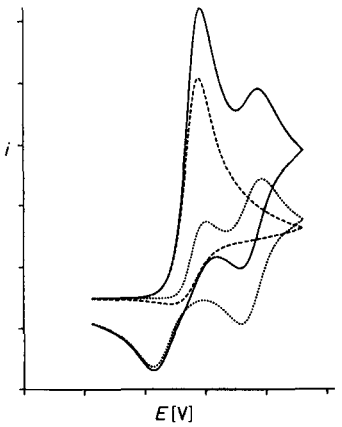


Fig. 19. Simulated cyclic voltammograms for the ECCEE mechanism: (—) complete cyclic voltammogram; (-----) cyclic voltammogram of the ECC reaction omitting the reduction of the electroactive follow-up product; (·····) reduction of the electroactive follow-up product (EE) in an ECCEE reaction.

Figure 19 gives an impression of the "fine structure" of the voltammogram of an ECCEE reaction. Accordingly, the first anodic peak essentially corresponds to the oxidation of the anion of the follow-up product **6**; in contrast, the first cathodic wave is composed of the reduction waves of **5** and **6**. The whole of the second wave of the cyclic voltammogram is the result of the formation of the dianions $6^{2\ominus}$.

5. Low Temperature Voltammetry

Recent developments have shown that low temperature experiments in voltammetry are extremely useful for qualitative and quantitative mechanistic studies.

Originally, low temperature experiments served to stabilize reactive intermediates whose existence could not be established on the time scale of cyclic voltammetry at room temperature[58]. The pioneering work of *Van Duyne* and *Reilley*[159] laid the experimental and theoretical basis for this technique. In their studies, the authors were able to prove, for the first time, that the instability of electrochemically produced radical cations is often due to the presence of nucleophilic impurities (H_2O) in the aprotic solvent or to the nucleophilic properties of the solvent itself (dimethylformamide, acetonitrile).

In recent studies low temperature voltammetry has been used to analyze conformational equilibria which precede electron transfer (CEE mechanism[160]). Since conformational isomers are usually separated by low activation barriers, this technique is the method of choice. So far, the thermodynamics and kinetics of the conformational interconversions of cyclic dialkylhydrazines[155] and vicinal dibromides[161,162] have been studied by cyclic voltammetry in butyronitrile at $T \leq -55$°C. However, a crucial prere-

quisite for the success of such experiments is that the heterogeneous electron-transfer reactions at the isomers, which have virtually identical redox potentials, occur at different rates, thereby facilitating the observation of separate current waves.

Although the determination of activation parameters has long been routine in experimental kinetics[163], examples are still rare in voltammetry. Measurements of the activation energies in the reductive dimerization of **2** and other anthracene derivatives (cf. Section 4.1.) are the best known examples, perhaps because the unexpectedly low activation energies and slow kinetics have generated an intense — and unresolved — controversy in the literature[114,115]. As an explanation for this finding, *Parker* et al.[114] postulated a two-step mechanism, the first of which is the formation of an intermediate complex; in contrast, *Savéant* et al.[115] take the view, based on the assumption of direct radical ion dimerization, that steric factors are responsible for the slow kinetics.

Heinze and *Schwart*[95] concluded from the change in the Arrhenius data for the reduction of 10-chloro-9-anthracenecarbonitrile **7** that there are two competing reactions (Fig. 20). Since then it has been shown that **7** is dimerized by reduction (EC_2...) and in a competing, parallel elimination of the halide (EC_1...) transformed into **2**[103,164].

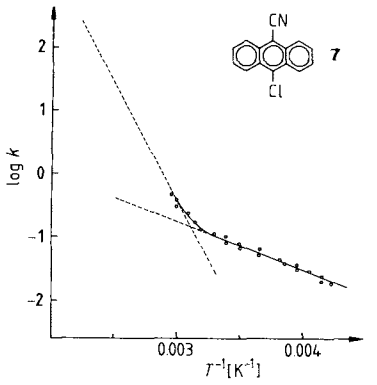


Fig. 20. Arrhenius plot for the decomposition of the radical anion of **7** (butyronitrile, [TBA]PF_6), experimental data from cyclic voltammetric experiments (+50 to −40°C).

Besides the kinetic perspectives, there have recently been indications that low temperature voltammetry may be used to characterize thermodynamic parameters. Reducing arenes in THF in the presence of $NaBPh_4$ as ground electrolyte, one observes in the cyclic voltammograms that with decreasing temperature there are large shifts in the redox waves of the multicharged anions in the cathodic direction[76,92] (Fig. 21). These effects result from a change in the ion pair equilibria caused by increasing solvent permittivity: at low temperatures they are transformed from contact ion pairs into solvent-separated ion pairs. In extreme cases this shift can amount to 600 mV. This corresponds to a change in the ion pair formation constant of ten orders of magnitude. Low temperature voltammetry, like the spectroscopic methods[165], has thus proved a sensitive tool for the study of ion pair effects.

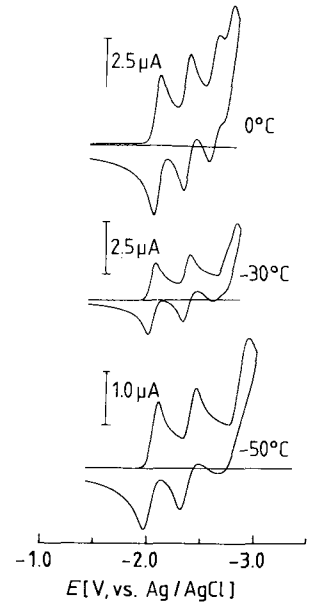


Fig. 21. Cyclic voltammograms for the reduction of 9,9'-bianthryl in THF/$NaBPh_4$ over the temperature range 0 to −50°C. Strong ion-pairing effects cause large cathodic shifts of the redox steps as the temperature decreases.

6. Digital Simulation

The variety of electrochemical reaction mechanisms and the individuality of the systems investigated reveal again and again that diagnostic criteria or known working curves are not sufficient for a quantitative evaluation of cyclic voltammetric experiments. Ambiguity is often removed only by completely calculating the current-voltage curves for different experimental parameters.

Numerical methods have proved themselves in the theoretical analysis of cyclic voltammograms[19,20]. Most of them are based on finite difference approximations[166], but over the last three years the use of finite element methods has been discussed[167–169], some variants of which are as efficient as the difference methods[170].

The finite difference approximations have become very popular due to their simplicity and clearness. *Feldberg*'s classical works[19,171] popularized them under the concept of *digital simulation*. The principle of the calculation is based on transforming the differential form of the mass transport equation [Eq. (4)] into a difference equation [Eq. (33)].

$$\frac{c_i'-c}{t'-t} \equiv \frac{\Delta c}{\Delta t} = \frac{D}{\Delta x^2}(c_{i+1}-2c_i+c_{i-1}) \qquad (33)$$

$i = 0, 1, 2, \ldots, N$

The mass transport problem is discretized in time and space. This means that within each respective time interval Δt the concentration values of the diffusion layer at i grid points at intervals Δx are calculated from the difference in the corresponding fluxes to and from each individual grid point (Fig. 22). The electrode process [heterogeneous charge-transfer—Eq. (3)] which controls the mass transport is a boundary condition of the simulation model. Coupled chemical reactions, as a rule the reason for simulations, are

taken into account in the difference model through the simple addition of the kinetic terms.

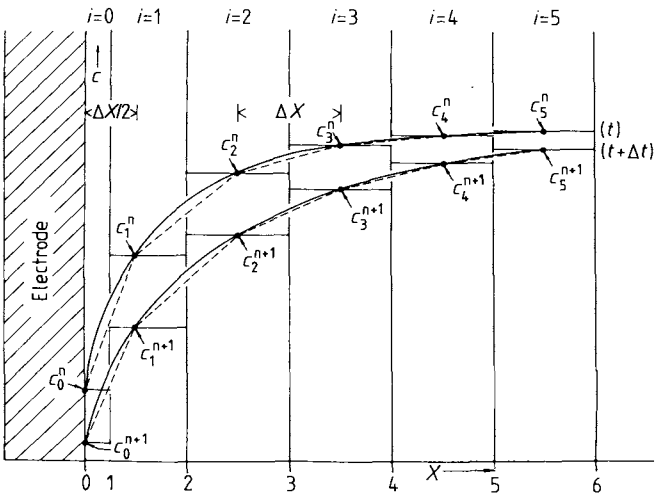


Fig. 22. Equidistant grid for the simulation of diffusive mass transport using finite difference approximation. The discrete values of a concentration profile are calculated in Δx intervals using Eq. (33) or (34).

In this way all important mechanisms can, in principle, be simulated numerically. However, the explicit method favored previously met with problems caused by computer time and stability for fast processes, both of which were never really overcome[172–175]. For this reason the use of implicit methods for digital simulation has gained ground, especially the efficient Crank-Nicholson technique[176, 177]. Whereas in explicit methods the new concentration values c_i' are determined point by point from the differences of the "old" concentrations [Eq. (33)], in the implicit method they are obtained by solving a system of simultaneous equations [Eq. (34)].

$$\frac{c_i'-c_i}{\Delta t}=\frac{D}{2\Delta x^2}(c_{i+1}'-2c_i'+c_{i-1}'+c_{i+1}-2c_i+c_{i-1}) \qquad (34)$$

$i=0, 1, 2, \ldots, N$

Although the associated computer programming is more complicated, the Cranck-Nicholson method is unconditionally stable and very accurate for all combinations of parameters. Furthermore, the computer time for the simulation of fast reactions is considerably shorter than with the explicit method.

7. Prospects

In recent years cyclic voltammetry has developed into an efficient technique for characterizing heterogeneous and homogeneous electron-transfer mechanisms.

In this article, space has not permitted more than a small selection of examples to be delineated, with emphasis being placed on organic reactions, but those selected should illustrate the *potential* of the method. The knowledge that numerous reactions which have so far been interpreted only in chemical terms are also coupled with electron transfer processes or catalyzed by them should ensure a wider field of application. Moreover, the quantification of measurements will become routine as soon as simulation programs and evaluation methods become available which can be fairly easily mastered by chemists without special mathematical training.

Two paths of potential development are already apparent. The increasing use of faster, more efficient data processing systems will promote new presentations of voltametric experiments, e.g. the convolutive or semi-integral technique[178–180] or derivative voltammetry[181]. These methods have considerable advantages over conventional voltammetry in that they simplify the acquisition and evaluation of kinetic data.

The prospective introduction of ultramicroelectrodes will in principle expand the measuring possibilities[52, 182]. Firstly, this will extend the time scale of voltammetry by two to three orders of magnitude. Secondly, the extremely small measuring currents will soon permit routine experiments in low-conductivity solutions, which will facilitate the study of electron-transfer reactions in solvent electrolyte systems virtually free of supporting electrolytes[65].

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Prostaglandin Syntheses by Three-Component Coupling

New Synthetic Methods (49)

By Ryoji Noyori* and Masaaki Suzuki

The role played by prostaglandins (PGs) in the human body is bewitching. Following the elucidation of their structures in the early 1960s, tremendous efforts were made for the realization of an efficient chemical synthesis, since a sufficient supply of such very rare, naturally occurring local hormones relies solely on their total synthesis. Of the many synthetic routes described in the literature, the majority of which are linear or sequential in nature, the Corey synthesis is perhaps the most versatile; so far more than 5000 prostaglandin analogues have been prepared and have been tested biologically. Some natural prostaglandins and their analogues are already in clinical use. In view of the continuing expansion of this field, we have been fascinated with the concept of developing a highly convergent entry to prostaglandins based on a new strategy. The discovery of a highly enantioselective method for the reduction of prochiral ketones and the elaboration of a procedure for double vicinal CC-coupling with enones have enabled a one-pot synthesis of the complete prostaglandin skeleton by linking a chiral 4-oxygenated 2-cyclopentenone unit and two side-chain blocks. This approach is efficient and flexible and allows the direct production of all the naturally occurring prostaglandins and a wide spectrum of analogues.

1. Introduction

Prostaglandins exhibit diverse pharmacological properties and are now recognized as local hormones that control a multitude of important physiological processes[1]. The chemical, biological, and medicinal investigations being carried out in this area stand in the forefront of the life sciences. Since the elucidation of the structure of the prostaglandins (Scheme 1) in the early 1960s, their chemical synthesis has occupied one of the central, exciting places in synthetic organic chemistry, because a total synthesis is the only means by which sufficient quantities of these

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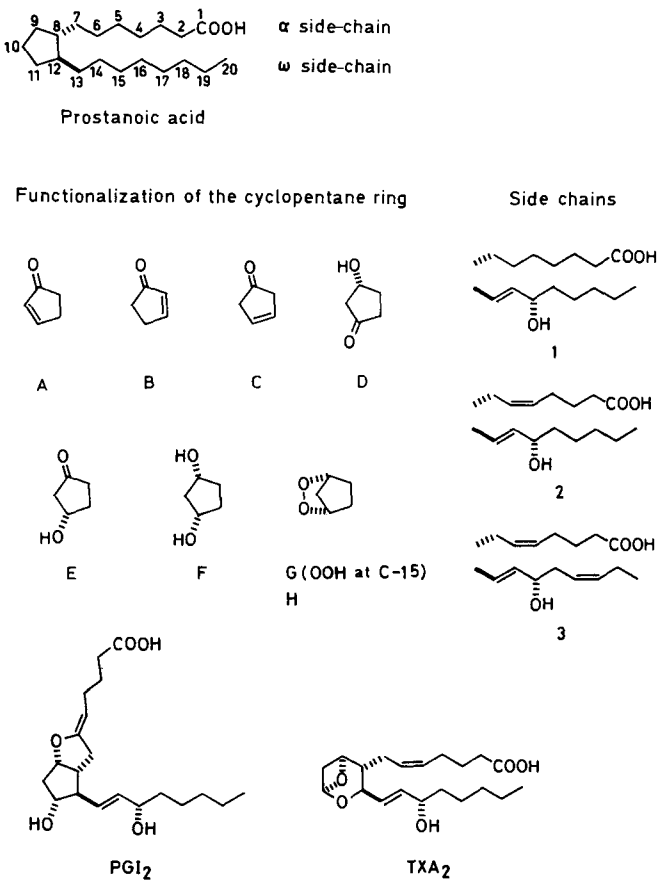
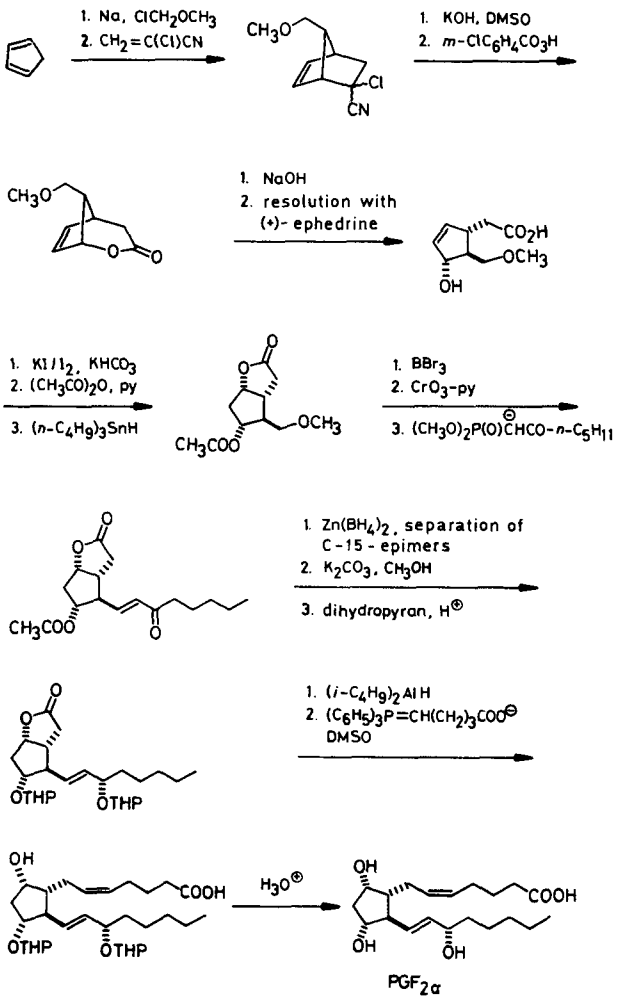
physiologically bewildering but rare, naturally occurring substances can be made available. Their biosynthesis simply cannot meet the ever increasing demand for these substances[2] nor provide adequate amounts of precursors for the production of medicinally important compounds possessing modified structures. A tremendous number of chemists have so far been involved in the synthesis of prostaglandins and more than 450 publications on this topic appeared in the literature up to 1982[3]. It is not the intention of this article, however, to present a comprehensive and detailed account of such works. Of the many elegant synthetic routes so far elaborated, the most practical are perhaps those outlined in Schemes 2 and 3. The former was developed in 1969 by *Corey* et al.[4], while the latter was first described in 1967 by *Just* et al.[5] and later established by the Upjohn Company[6]. These two synthetic strategies are feasible on a large scale (up to 50 kg of $PGF_{2\alpha}$ or equivalent compounds per year) and are more than one hundred times as effective as the biosynthetic pathway using crude enzymes and polyunsaturated fatty acid substrates such as arachidonic acid or dihomo-γ-linolenic acid[1d].



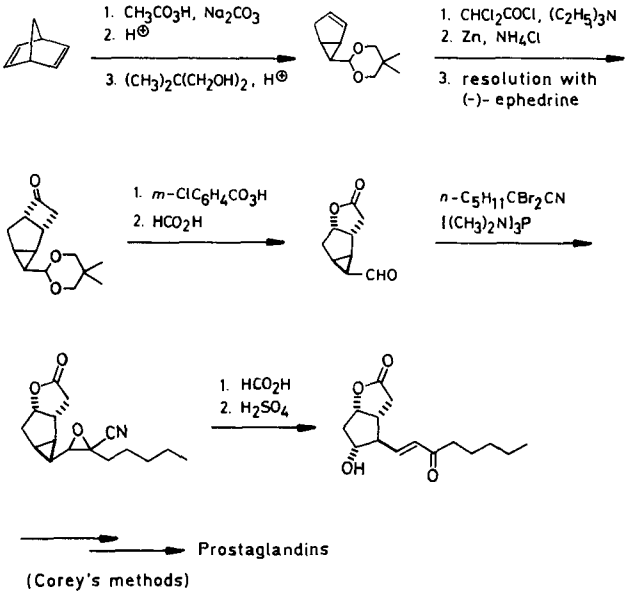
Scheme 1. Classification of the prostaglandins (PG). PGI_2 and TXA_2 are prostacyclin and thromboxane A_2, respectively.

Both methods cleverly solved the main problems in prostaglandin synthesis: 1) selective creation of the four or five asymmetric centers in the prostaglandins of the E and F series, respectively, 2) stereoselective insertion of the CC



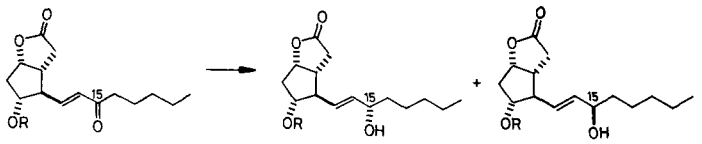
Scheme 2. *Corey*'s prostaglandin synthesis. DMSO = dimethyl sulfoxide.

double bonds, and 3) overcoming the instability of the β-hydroxycyclopentanone structures in prostaglandins. Since these routes start with cyclopentadiene or norbornadiene,



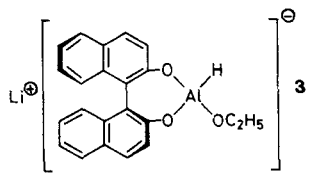
Scheme 3. The Just-Upjohn procedure.

rigid bicyclic intermediates are formed, which make the perfect stereochemical control about the five-membered ring possible. A number of other routes for the preparation of such versatile lactone intermediates are also known. Stereoselective formation of the C=C bonds can be achieved by Wittig-type condensation. The unstable hydroxy ketone unit in the prostaglandins of the E series is constructed at the final stage of the synthesis. A long-standing problem in the original procedure was a lack of means of controlling the absolute stereochemistry at C-15; the customary industrial processes include hydride reduction of the enones of type **1** and tedious chromatographic separation of the resulting C-15-epimeric alcohols (*S*)-**2** and (*R*)-**2** (Scheme 4).



Scheme 4. Reduction of the Corey lactone **1d**. THP = tetrahydropyranyl.

In endeavoring to solve this problem, *Corey* et al. found that reduction of the enone **1a** having a special protective group at C-11 with a reagent prepared from (+)- or (±)-limonene, thexylborane[7], and *tert*-butyllithium at −120 °C affords the alcohols (*S*)-**2a** and (*R*)-**2a** in the ratio 92 : 8[8]. Recently developed methodologies provide practical solutions to this problem. The chiral aluminum hydride reagent **3** discovered in our laboratories enables the highly stereoselective reduction of **1b** — **1d** to give the desired products (*S*)-**2b** to (*S*)-**2d**[9]. Regardless of the nature of the protective groups at position 11 or whether or not the hydroxyl function is protected, the *S*/*R* ratio is generally greater than 99%. This reagent is far more stereoselective than any of the other known reagents. The Ono group as well as *Yamamoto* et al. have reported that the unprotected enone **1d** could be reduced with a large excess of diisobutylaluminum hydride modified with 2,6-di-*tert*-butyl-4-methylphenol to give (*S*)-**2d** and (*R*)-**2d** in the ratio 92 : 8[10].

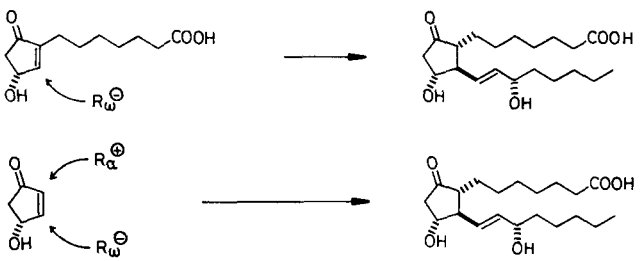


Prostaglandin endoperoxides PGH_2[11] and PGG_2[12] as well as prostacyclin (PGI_2)[13] have been prepared by way of $PGF_{2\alpha}$. The extremely unstable thromboxane A_2 (TXA_2, Scheme 1), however, has not yet been synthesized. The processes outlined in Schemes 2 and 3 are flexible and not only enable the synthesis of natural prostaglandins but also of a great number of analogues. Consequently, the total synthesis constitutes a notable landmark in the progress of modern organic chemistry; it has made a great contribution to the advancement of our knowledge on the biological properties of the prostaglandins.

2. Approaches Involving Conjugate Addition

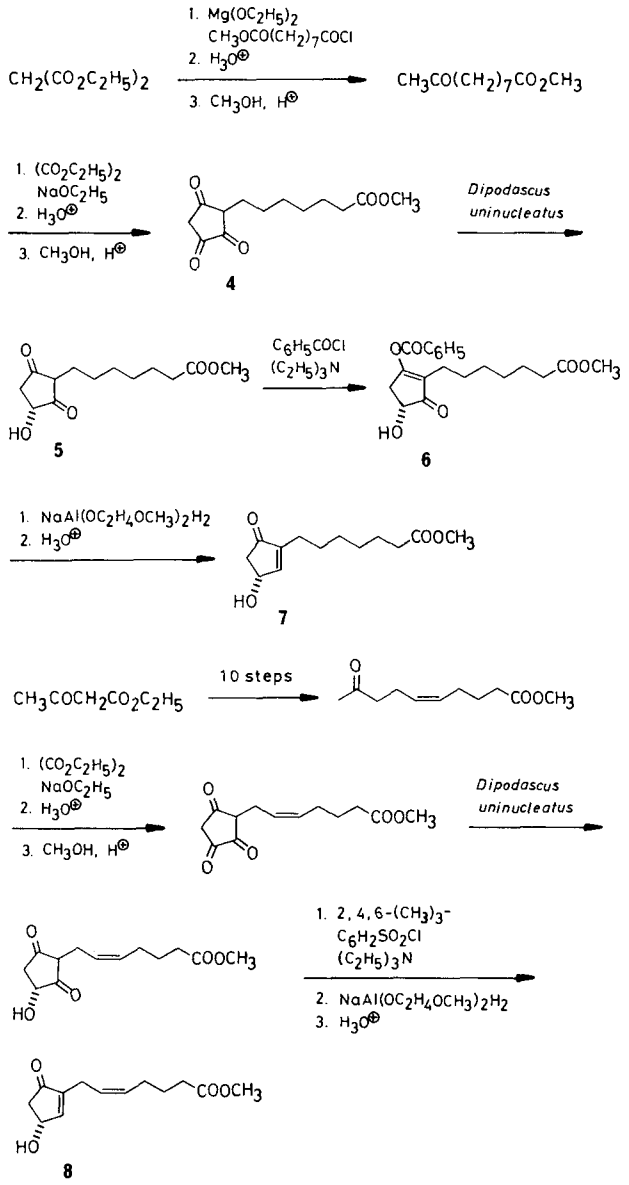
The approaches depicted in Schemes 2 and 3 are classified as linear or sequential syntheses, in which the whole structure is constructed step-by-step. *Corey*'s route involves 17 steps for the preparation of (±)-$PGF_{2\alpha}$ from cyclopentadiene, and 19 steps for the synthesis of (±)-PGE_1. Four synthetic steps are required for the formation of the five carbon-carbon bonds, while the remaining 13 to 16 steps constitute functional group transformations such as oxidation, reduction, protection, deprotection, etc. The Just-Upjohn synthesis also proceeds via the *Corey* lactone **1d** and requires a total of 16 steps from norbornadiene to (±)-$PGF_{2\alpha}$, of which three are required for the creation of the carbon-carbon bonds. In addition, optical resolution is conducted at the stage of the lactone intermediate so as to obtain the naturally occurring forms.

The above described procedures are clearly successful. However, shorter, highly convergent entries via a combination of suitably chosen building blocks are obviously much more desirable. In this context, approaches involving "conjugate addition" are among the most attractive and have been studied extensively since the early days of the synthetic investigation. The obvious dissection of the prostanoic acid skeleton would immediately suggest two possible routes for this strategy (Scheme 5): 1) introduction of



Scheme 5. Prostaglandin syntheses via conjugate additions.

the "lower" side chain (ω side-chain) into a 4-hydroxy-2-cyclopentenone which already possesses the "upper" side chain (α side-chain), and 2) the consecutive linking of ω and α side-chains to cyclopentenones. In both cases, nucleophilic introduction of the ω side-chain into a 2-cyclopentenone with formation of the bond between C-12 and C-13 provides an obvious route for this purpose; hereby, organometallic chemistry plays an important role. Many other synthetic routes are conceivable but would perhaps require the development of some new synthetic methodologies. Several methods providing access to the chiral cyclopentenone intermediates have been elaborated. *Sih* et al. have used microbiological asymmetric reactions (Scheme 6)[14]. First, the triketone **4** was prepared in 75—80% yield by sodium ethoxide-catalyzed condensation of methyl 9-oxodecanoate and ethyl oxalate. Of the various microbes investigated, *Dipodascus uninucleatus* was found

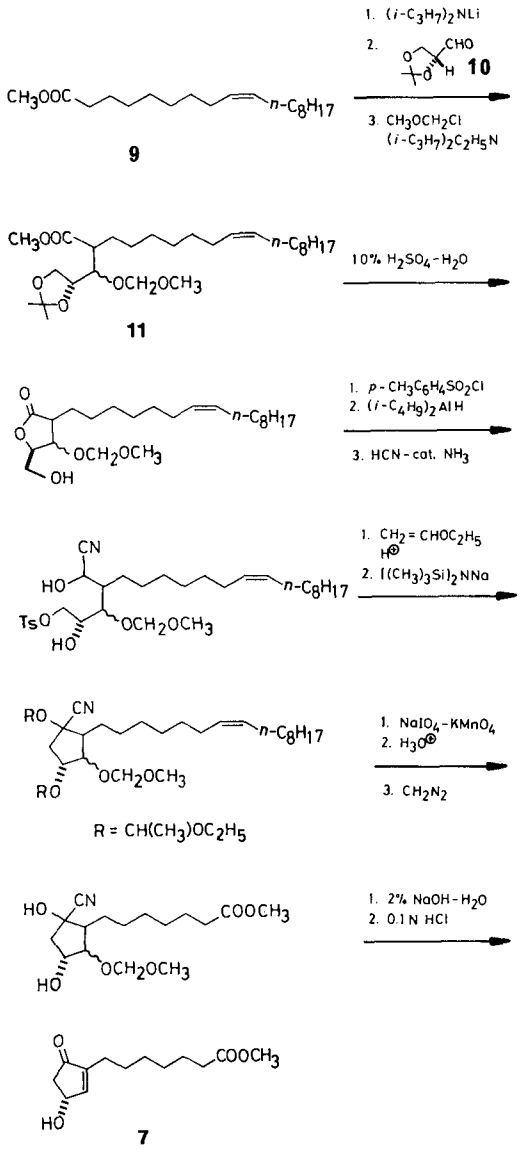


Scheme 6. Synthesis of 2-substituted (*R*)-4-hydroxy-2-cyclopentenones 7 and 8 via asymmetric microbial reactions.

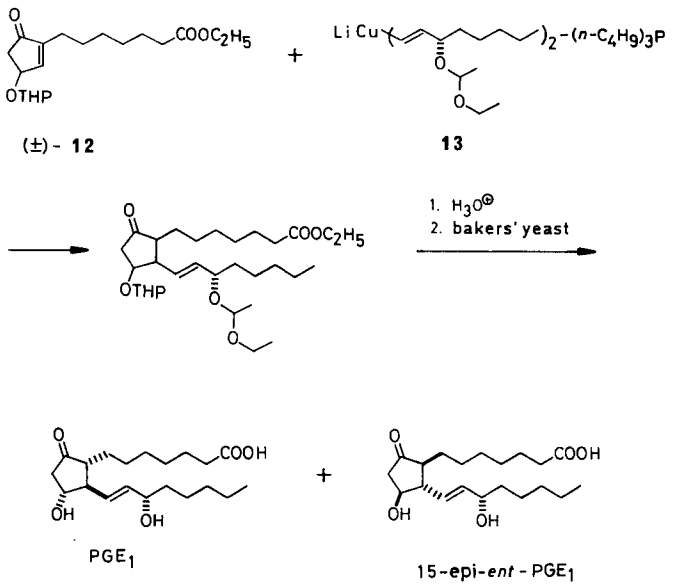
to be the most suitable for reducing the triketone **4** in a soybean-glucose medium to the optically pure (4*R*)-hydroxy diketone **5** (75% chemical yield). The partial asymmetric hydrogenation was achieved with a soluble chiral catalyst, (1,5-cyclooctadiene)bis[cyclohexyl(*o*-methoxyphenyl)methylphosphane]rhodium(I) tetrafluoroborate, giving **5** in 75% yield and 30% optical purity. Recrystallization increased the optical purity of **5** to 68%. Selective benzoylation of the β-diketone, giving **6** (70%), followed by reduction with sodium bis(2-methoxyethoxy)dihydridoaluminate and debenzoylation afforded without racemization the chiral hydroxyenone **7** in 60% yield (21% referred to **4**). In a similar manner, the hydroxy enone **8** with unsaturated α side chain was prepared via 17 steps in 4% overall yield (referred to the educt ethyl acetoacetate).

Stork and *Takahashi* used D-glyceraldehyde as chiral source for securing the (4*R*)-configuration (Scheme 7)[15]. A base-catalyzed condensation of the unsaturated ester **9** with protected D-glyceraldehyde **10** was followed by methoxymethylation of the resulting alcohol to the ether **11**. Subsequent acid-catalyzed lactonization and multistep carbocycle formation gives ultimately the desired cyclopentenone **7**. The chiral building blocks **7** and **8** are also accessible by resolution[16] of the racemates[17,20b,21], by multistep synthesis using a resolved intermediate[18], or by enzymatic oxygenation of a 2-substituted 2-cyclopentenone[19].

In 1972, *Sih* et al. reported for the first time on a successful prostaglandin synthesis of this type (Scheme 8)[20]. The chiral cuprate **13**, prepared from the organolithium derivative of the ω side chain, was condensed with (±)-**12** at 0°C in ether. After removal of the alcohol protective group and hydrolysis of the ester by bakers' yeast, PGE_1 (21%) and 15-epi-*ent*-PGE_1 (23%) were obtained. The organocuprate apparently attacks the five-membered ring from the less hindered side. In addition, when a small quantity of unprotected (±)-**7** is present, some 11,15-epi-*ent*-PGE_1 is also formed. The vinylogous addition of the cuprate to the optically active cyclopentenone derivative **14** afforded,

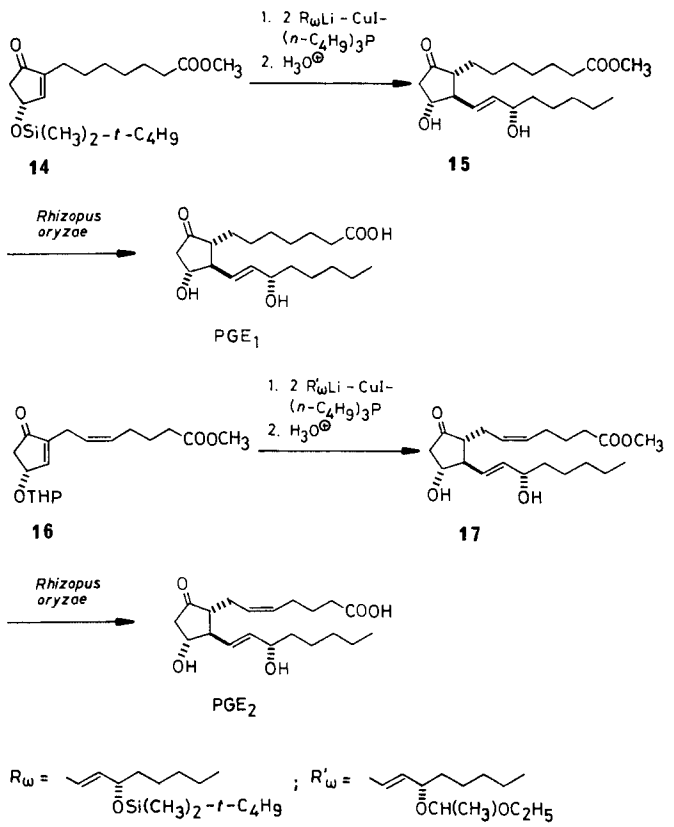


Scheme 7. Synthesis of the optically active 2-substituted (*R*)-4-hydroxy-2-cyclopentenone 7 from D-glyceraldehyde.



Scheme 8. Synthesis of PGE_1 by conjugate cuprate addition.

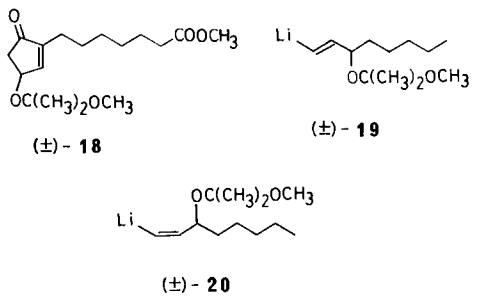
after deprotection, the PGE_1 methyl ester **15** in 60% yield (Scheme 9)[14].



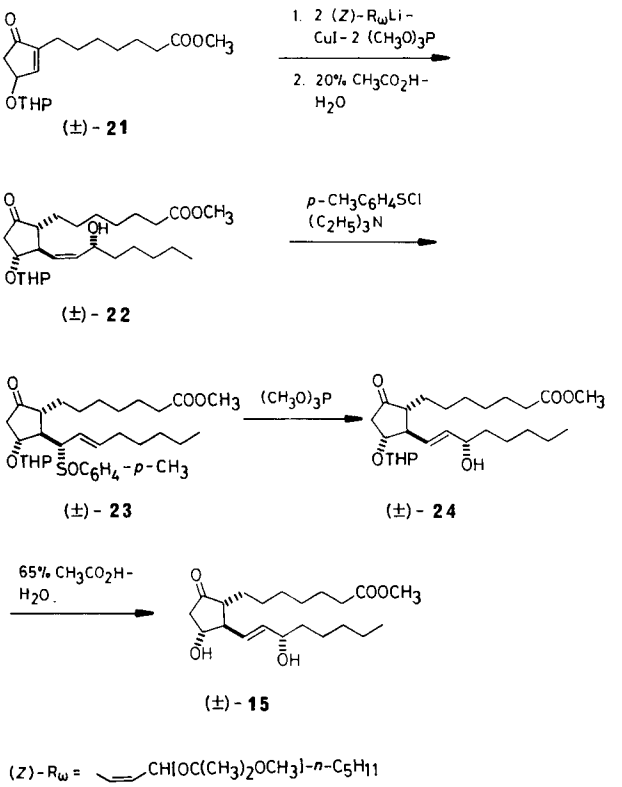
Scheme 9. Synthesis of PGE_1 and PGE_2 via the two-component coupling process.

Among a variety of organocopper reagents examined, the cuprate generated from the $(n\text{-}C_4H_9)_3P$–CuI complex and vinyllithium (molar ratio 1:2) was found to be the most effective. The ester **15** was hydrolyzed with the microorganism *Rhizopus oryzae* to give PGE_1 in 95% yield. In a similar manner, the cyclopentenone **16** afforded the methyl ester **17** in 50% yield. Enzymatic hydrolysis of **17** gave PGE_2 in 82% yield[14].

Independently, a Syntex group chose a similar strategy but with different cuprate reagents[21]. Reactions of the protected 2-cyclopentenone derivative (±)-**18** with an organocuprate reagent formed from $CuI[(CH_3O)_3P]_2$ and the (*E*)-vinyllithium compound (±)-**19** furnished the desired product of a conjugate addition only in very low yield; after alcohol deprotection, methyl esters of (±)-PGE_1 (1%) and (±)-15-epi-PGE_1 (0.3%) were obtained together with 80% of recovered 4-hydroxy-2-cyclopentenone derivative (±)-**7**. However, when the (*Z*)-cuprates, formed from the (*Z*)-vinyllithium compounds (±)-**20** (the corresponding

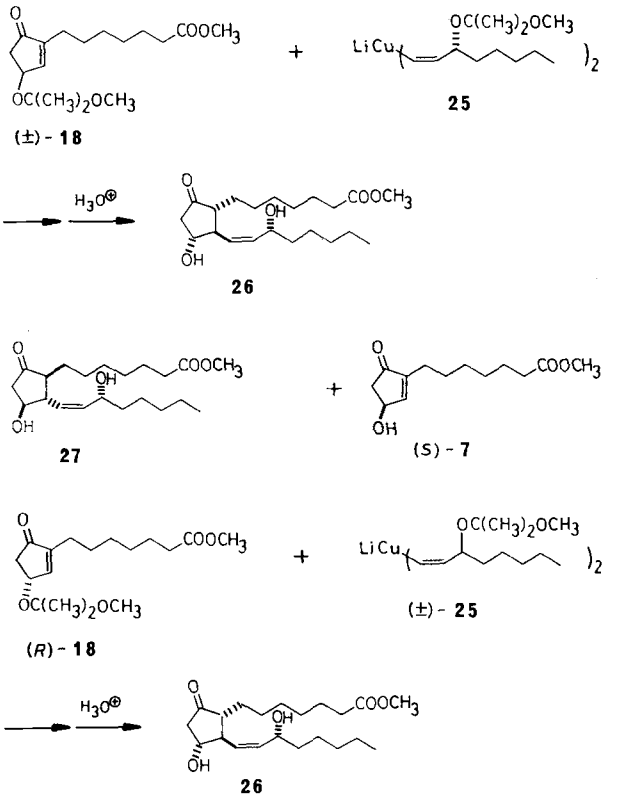


iodoallyl alcohol is accessible in ca. 65% yield from the propynol), were used in the vinylogous addition to (±)-**21**, the adduct (±)-**22** was obtained in 45% yield, the 15*R*/15*S* ratio being >97:3 (Scheme 10)[22]. The requisite inversion of the configuration of the OH-groups on C-15 was accomplished by the procedure of *Evans* et al.[23], via the steps



Scheme 10. Prostaglandin synthesis by conjugate addition of a (*Z*)-vinyl cuprate.

22 → **23** → **24**, in 71% total yield. The chirality of the carbon was transferred with perfect stereocontrol, and no trace of the isomer with 13*Z*,15*R*-configuration was detected. After removal of the tetrahydropyranyl protecting groups, the racemic PGE_1 methyl ester (±)-**15** was obtained in 90% yield.

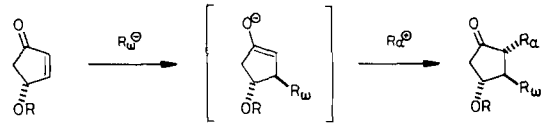


Scheme 11. Kinetic resolution by conjugate addition of a (*Z*)-vinyl cuprate.

The high degree of diastereoselectivity of the conjugate cuprate addition enables the kinetic resolution of racemic 2-cyclopentenones or ω side chains by chiral counterparts (Scheme 11). The Syntex group and *Stork* found that reaction of the racemic cyclopentenone (±)-**18** with the optically active cuprate **25** (molar ratio 1:3) gave an 86:14 mixture of **26** and **27** together with ca. 30% of unreacted (*S*)-**7**[21c,22]. Later, *Stork* and *Takahashi* carried out this reaction by combining one equivalent of the optically active enone (*R*)-**18** and three equivalents of the racemic cuprate (±)-**25**; they obtained a single stereoisomer (**26**), thus confirming complete kinetic resolution[15]. In the reaction of the optically active (*E*)-cuprate and the racemic enone (±)-**18**, no noticeable kinetic resolution took place[20].

The organocuprate-mediated method was also applied to the synthesis of racemic PGD_1[24]. Such attempts were also made with organoaluminum compounds and with Grignard reagents in the presence of copper salt catalysts[25]. In principle, such synthetic routes via two-component coupling processes have paved the way but, as yet, they do not appear to be industrially viable. The major practical problems encountered in this approach are: 1) the lack of efficient ways to obtain the key chiral cyclopentenones, and 2) the inefficiency of the direct introduction of "natural" (*E*)-alkenyl side-chains by conjugate addition procedures.

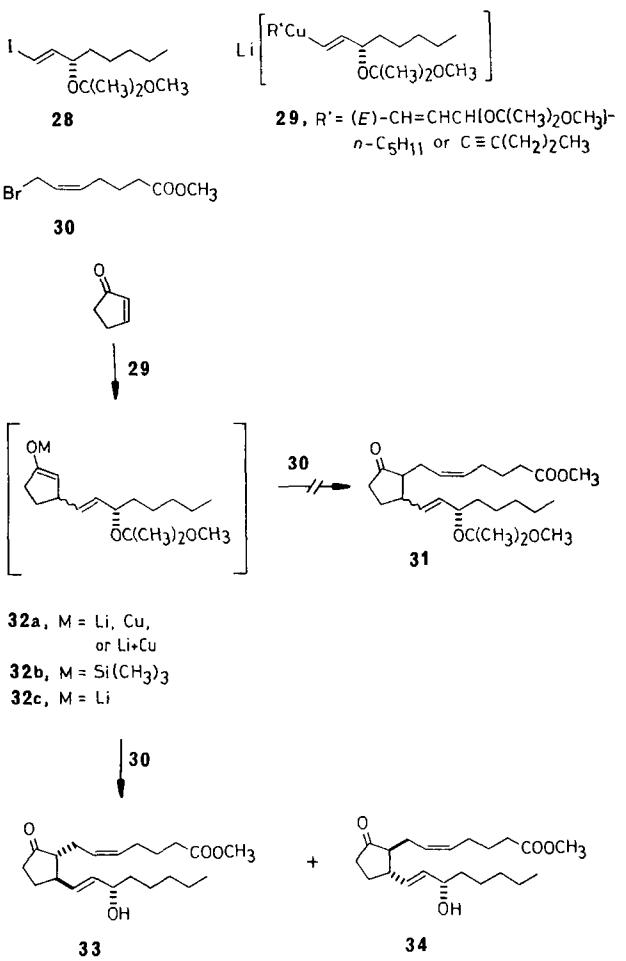
The three-component coupling process, namely, a single-pot combination of a five-membered ring unit and the two side chains would be the ultimate goal in effective prostaglandin syntheses. Such entries, if feasible, are superior to other methods in view of their directness and high flexibility. Scheme 12 actualizes the concept by way



Scheme 12. Basic strategy of the three-component coupling process.

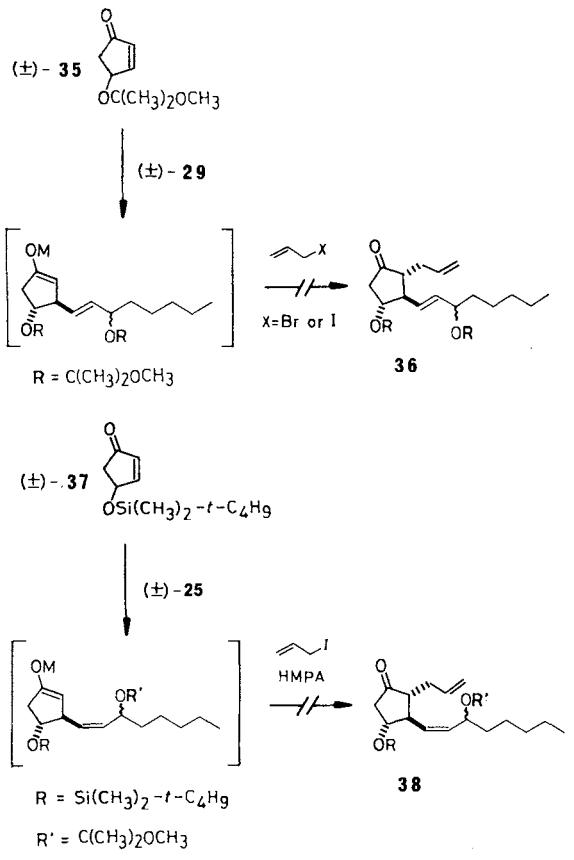
of example of the nucleophilic transfer of the ω side-chain unit to a protected 4-hydroxy-2-cyclopentenone followed by electrophilic assembling of an α side-chain equivalent. At first sight, this approach looks very simple, but, when we started our investigations, very little success had been obtained with such a strategy.

Since organocuprate reagents have been widely used for the addition of organic groups to the β-position of α,β-unsaturated ketones[26], one may simply expect that the cuprate-mediated conjugate addition of an ω side-chain block to a 4-oxygenated 2-cyclopentenone followed by al-



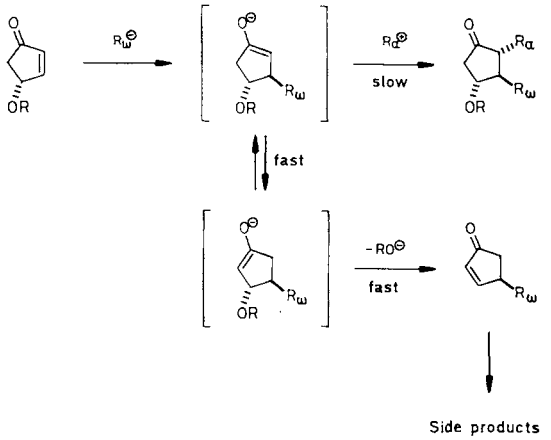
Scheme 13. Attempted double vicinal CC-coupling with 2-cyclopentenone.

kylation of the enolate intermediate with α side-chain halides could lead directly to PGE derivatives. In reality, however, such processes appear to be quite difficult to realize. In 1974, a Syntex research group was the first to report the results of model experiments for double vicinal CC-coupling with 2-cyclopentenones (Scheme 13)[27]. Symmetrical or mixed vinyl cuprates **29** were prepared from the (*E*)-configurated iodide **28**. However, vinylogous addition of **29** to unsubstituted 2-cyclopentenone and subsequent reaction with the allyl bromide **30** failed to give the condensation product **31**, even though a variety of conditions were tested. The enolate **32a** formed initially was then converted into the trimethylsilyl ether **32b**. Regeneration of the lithium enolate **32c** by lithium amide in liquid ammonia followed by trapping with two equivalents of the bromide **30** at −35°C gave, after deprotection, methyl esters of 11-deoxy-PGE_2 **33** and 11-deoxy-8,12-epi-PGE_2 **34** in 17 and 13% yield, respectively. Reaction of the lithium enolate (±)-**32c** with methyl 7-iodo-5-heptynoate furnished a diastereomeric mixture of the corresponding alkynes in 19.5% yield. Other Syntex chemists examined in detail the possibility of a direct linking of three synthetic building blocks using an (*E*)- or (*Z*)-vinyl cuprate; they reconfirmed the previously encountered difficulties (Scheme 14)[28]. When the racemic 4-hydroxy-2-cyclopentenone derivative (±)-**35** was subjected to the conjugate addition using two equivalents of the (*E*)-cuprate (±)-**29** in ether, and then to reaction with 1.1 equivalents of allyl bromide or iodide in the presence of 15 vol-% hexamethylphosphoric triamide, no trace of the desired product **36** was obtained.



Scheme 14. Attempted double vicinal CC-coupling with protected 4-hydroxy-2-cyclopentenones. HMPA = hexamethylphosphoric triamide.

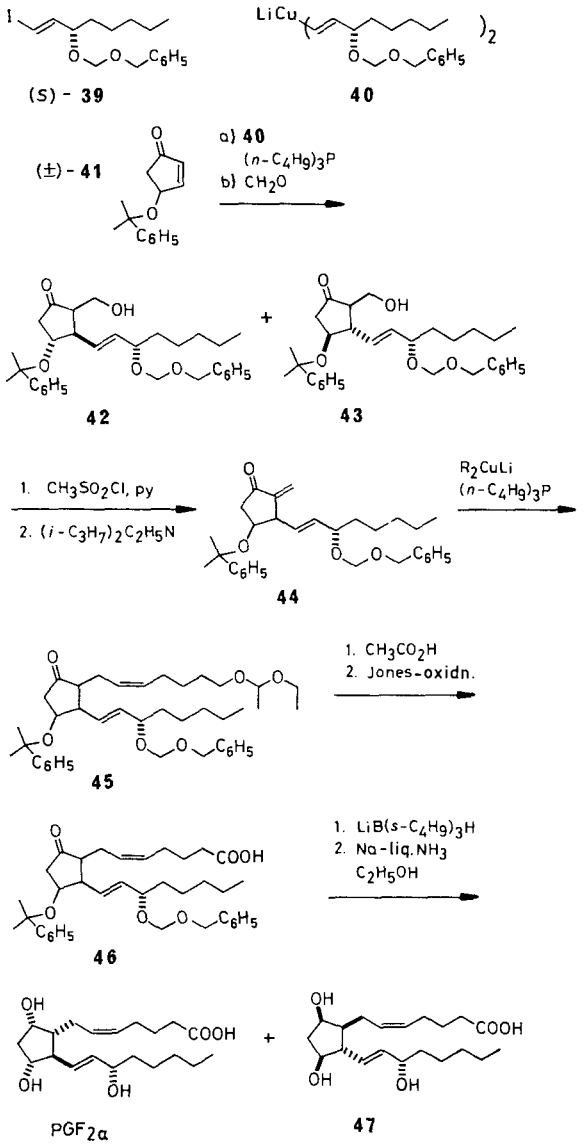
An attempt with the silyl protected cyclopentenone (±)-**37** and two equivalents of the (*Z*)-vinyl cuprate (±)-**25** also did not afford the allylation product **38**. The failure of these attempts is presumably due to the complex nature of the reaction system[29], in which an equilibration of the enolates and a cleavage of water from the five-membered ring can take place concomitantly (Scheme 15). The proton transfer occurs at a rate faster than the desired regiospecific alkylation reaction. The cuprate-generated intermediate species could be a lithium enolate, but the presence of copper salts and other ligands might retard the alkylation with organic halides.



Scheme 15. Equilibration of intermediates of the cuprate addition.

In the mid 1970's, investigations along these lines were shifted to the development of somewhat modified, indirect routes. In 1975, *Stork* and *Isobe* reported a successful synthesis of $PGF_{2\alpha}$ (Scheme 16)[30]. They first converted the optically active (*E*)-vinyl iodide **39** into the lithium cuprate **40** by reaction of the lithium compound with the complex $(n\text{-}C_4H_9)_3P\text{—}CuI$ (molar ratio 2 : 1) in ether. Conjugate addition of **40** to one equivalent of the racemic α,α-dimethylbenzyl-protected hydroxy enone (±)-**41** was then carried out in ether at −78 to −20°C and the resulting enolate formed under kinetic control was trapped by about four equivalents of monomeric formaldehyde[31], an unusually powerful electrophile, in the same solvent at −78 to −50°C to produce a mixture of **42** (28—34%) and **43** (22—26%).

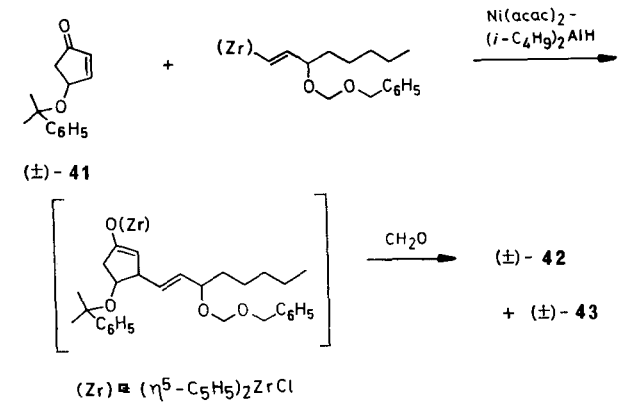
Dehydration of the adducts, to give the 2-methylenecyclopentanones **44**, followed by the second conjugate addition of a (*Z*)-vinyl cuprate led to the C_{20}-skeleton **45** with extended α-chain. Acid-catalyzed removal of the alcohol protecting group at C-1 and subsequent Jones oxidation gave the prostanoic acid **46**. Stereoselective reduction of the 9-keto function with lithium tri-*sec*-butyl hydridoborate to give the 9α-alcohol and subsequent removal of the C-11-protecting group by sodium metal dissolved in a liquid ammonia/ethanol mixture led to a stereoisomeric mixture of $PGF_{2\alpha}$ and 15-epi-*ent*-$PGF_{2\alpha}$ **47**. A pure sample of natural $PGF_{2\alpha}$ was obtained by chromatographic separation of the methyl esters and alkaline hydrolysis. The authors claim that the overall yields of $PGF_{2\alpha}$ and 15-epi-*ent*-$PGF_{2\alpha}$ **47** are approximately 9% and 7%, respectively (referred to **41**). Instead of the cuprate reagents, *Schwartz* et



R = (*Z*)-CH=CH(CH$_2$)$_3$CH$_2$OCH(CH$_3$)OC$_2$H$_5$

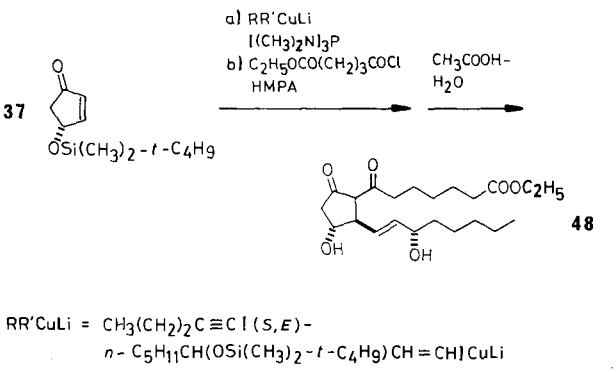
Scheme 16. The Stork-Isobe synthesis of PGF$_{2\alpha}$.

al. used a zirconium compound combined with a nickel catalyst for the conjugate addition reaction[32]. By this method, a mixture of racemic **42** and **43** was obtained in 69% yield (Scheme 17).



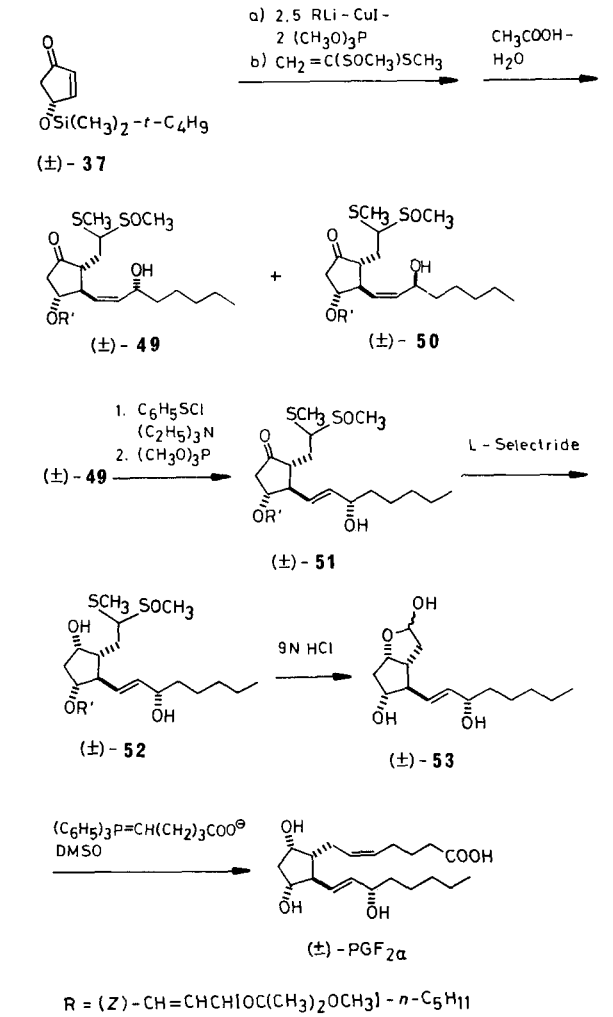
Scheme 17. Synthesis of the prostaglandin intermediates **42** and **43** via organozirconium reagents.

A Teijin research group found that reaction of acid chlorides with enolates formed from enones and mixed cuprates[33] occurs at the C-termini. The 7-oxo-PGE$_1$ derivative **48** was obtained in this way (Scheme 18)[34].



Scheme 18. Reaction of an organocuprate-generated enolate with an acyl chloride.

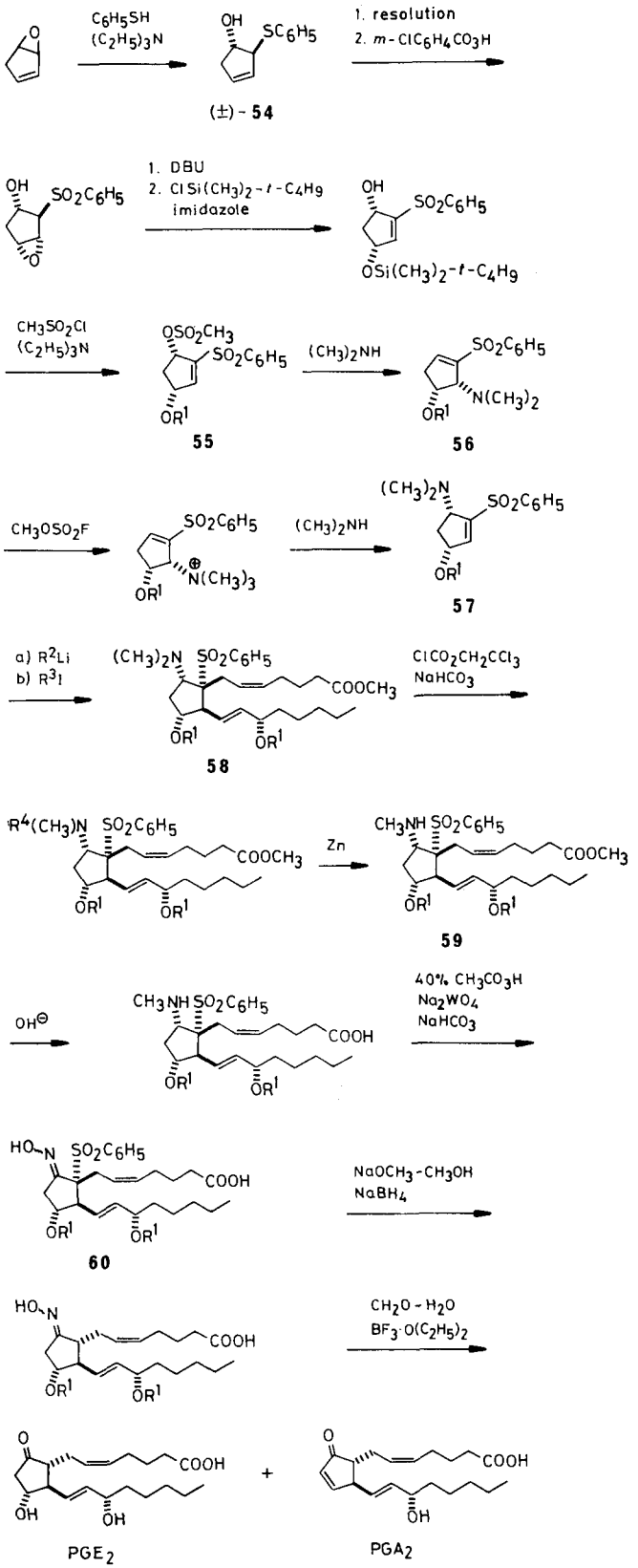
As first demonstrated by a Syntex group in 1979, some Michael acceptors that are synthetically convertible into PG α side chains can also serve as trapping agents for the enolate intermediates formed under kinetic control



R = (*Z*)-CH=CHCH[OC(CH$_3$)$_2$OCH$_3$]-*n*-C$_5$H$_{11}$

R' = Si(CH$_3$)$_2$-*t*-C$_4$H$_9$

Scheme 19. Prostaglandin synthesis via Michael-trapping of the organocuprate-generated enolate. L-Selectide = lithium tri-*sec*-butyl hydridoborate.



Scheme 20. Synthesis of PGE_2 according to *Fuchs* et al. DBU = diazabicycloundecane.

(Scheme 19)[28]. Reaction of the phosphite-complexed (*Z*)-divinyl cuprate (±)-**25** with the racemic enone **37** (1.4:1 ratio) in ether and subsequent treatment with two equivalents of 1,1-bis(methylthio)ethene *S*-oxide, an efficient Michael acceptor originally introduced by *Schlessinger* et al.[35], at −78 to 0 °C afforded (±)-**49** in 45% yield together with a small amount (8%) of the 15-epimer (±)-**50**. In the Michael addition reaction, which leads to a racemic (13*Z*,15*R*)-isomers, a high degree of diastereoselectivity is noticeable[15,21c,22]. The 4-siloxy group was not eliminated during the reaction. A sulfenate-sulfoxide sigmatropic rearrangement[22,23] corrected the stereochemistry of the major product and led to the racemic (13*E*,15*S*)-isomer (±)-**51**. Stereoselective reduction of the 9-keto group by L-Selectride gave (±)-**52** in 95% yield. Since the dithioacetal monoxide functionality is a masked aldehyde, (±)-**52** could be converted with hydrochloric acid into the lactol (±)-**53**, which, in turn, was converted into racemic $PGF_{2\alpha}$ by the procedure of *Corey* et al.[4]. The overall yield from (±)-**37** to (±)-$PGF_{2\alpha}$ was 18%.

Fuchs et al. have reported a different type of triply convergent synthesis of PGE_2 (Scheme 20)[36]. Instead of the protected 4-hydroxy-2-cyclopentenone derivatives, they employed a cyclopentenyl sulfone, which is later converted into the desired ketol structure. The racemic alcohol (±)-**54**[37], formed by ring-opening of cyclopentadiene monoepoxide with thiophenol and triethylamine, can be resolved into its enantiomers[38] by the method of *Pirkle* et al.[39]. The seven-step conversion of (+)-**54** having correct stereochemistry led to the functionalized cyclopentenyl sulfone **57**, a key chiral intermediate, in 64% yield. A stereospecific Lawton-type S_N2'-displacement[40] of the cyclopentenyl sulfone (**55** → **56**) plays an important role in this sequence. Consecutive conjugate addition (in tetrahydrofuran (THF)/hexane at −60 °C) of a chiral vinyllithium compound corresponding to the ω side-chain and in situ alkylation of the resulting sulfonyl-stabilized carbanion with a C_7-allylic iodide having an α side-chain structure afforded the C_{20}-skeleton **58** in 67% yield. The stereochemical control at C-12 (PG numbering) was at least 97%. Treatment of **58** with trichloroethyl chloroformate followed by reduction with zinc gave the *N*-demethylated product **59**. Alkaline hydrolysis of the ester function and oxidation of the methylamino function with peracetic acid with added sodium tungstate catalyst gave the oxime **60**. Stereospecific reductive desulfonation, deoximation, and alcohol deblocking completed the synthesis of PGE_2. In the deoximation step, some β-elimination took place and ca. 10% of PGA_2 was formed as a byproduct. This prostaglandin synthesis starting from (±)-**54** requires 15 steps and an optical resolution. The overall yield is 13%.

3. The Three-Component Coupling Process

In spite of the discouraging results recorded by pioneers in this field, our interest was still fostered by the possibility of constructing the prostanoic acid framework in a single-step (Scheme 12) and, thereby, of realizing our goal—a direct, convergent PG synthesis. It emerged that: 1) a reliable method, which enables combination of the five-membered

enone unit and the ω and α side-chain units to give the complete C_{20}-carboxylic acid skeleton, had to be developed, and 2) easy access to chiral building blocks with the natural (11*R*,15*S*)-configuration had to be created. It seems reasonable to assume that generation of the (12*R*)-configuration is strongly controlled by the direction of the nucleophilic attack of the ω side-chain (*trans* to the substituents on C-4 of the cyclopentenone). The (8*R*)-configuration should also be favored kinetically or, even if not, this could be accomplished by some thermodynamically controlled operations.

3.1. Access to Optically Active Building Blocks

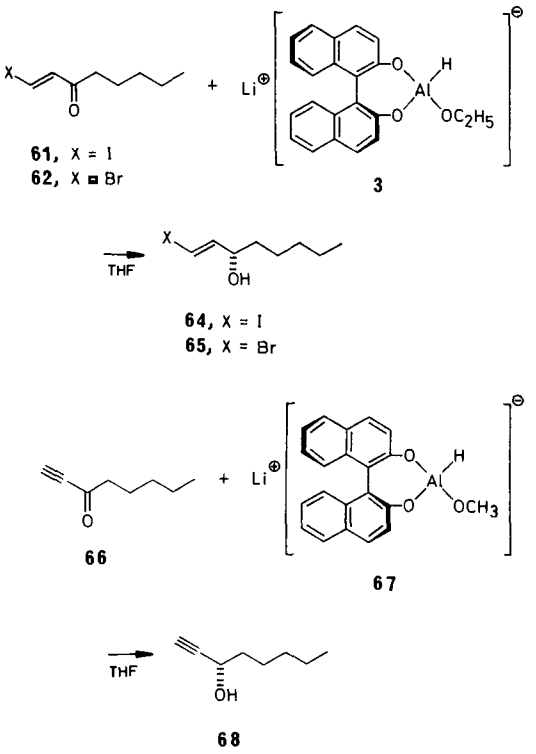
The racemic iodovinyl alcohol (±)-**64** having the ω side-chain structure was first prepared by *Corey* and *Beams*[33] and a Syntex group[21b] by hydride reduction of the iodovinyl ketone **61**, which is readily obtainable from the chlorovinyl ketone **63** by halogen exchange with sodium iodide. The bromoallyl alcohol (±)-**62** was prepared in a similar manner[25b]. Both alcohols were resolved via their hydrogen phthalates with (−)-1-phenylethylamine; the requisite (3*S*)-alcohols were obtained in 10% yield (referred to the racemates)[21b].

61, X = I
62, X = Br
63, X = Cl

(±)-**64**, X = I
(±)-**65**, X = Br

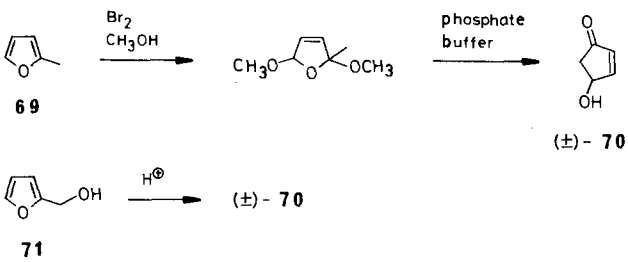
Sih et al. have carried out the microbiological reduction of **61** with *Penicillium decumbens* and obtained the (3*S*)-alcohol with an optical purity of 74%, but only in 10% chemical yield[14c]. We found that asymmetric reduction using the chiral BINAL-H reagent is far superior to such methods[9]. Thus, as shown in Scheme 21, the reduction of the prochiral ketones **61** and **62** with **3** gave the desired optically active alcohols **64** and **65** in 97 and 96% *ee*, respectively, and in high chemical yield (>95%). The iodoallyl alcohol **64** was likewise prepared by hydroalumination of the optically active acetylenic alcohol **68** and subsequent treatment with iodine (yield 47%)[20b]. Hydroboration instead of hydroalumination led to **64** in 42% yield[21b]. Optically active **68** was accessible by a classical resolution method[41], but asymmetric reduction proved to be much more efficient. Reduction of **66** with the BINAL-H reagent **67** in THF at low temperature gave **68** (84% optical purity) in 87% yield[42, 114d]. Reduction of **66** with *Midland*'s alpine-borane reagent led to **68** in 92% *ee* (65% yield)[43a]. *Mukaiyama* and *Suzuki* prepared trimethylsilyl-protected **68** (76% *ee*, 87% yield)[44] by condensation of lithium trimethylsilylacetylide and hexanal in the presence of a chiral auxiliary reagent.

The optically active cyclopentenone building blocks can be obtained in various ways: by resolution of the racemic hydroxy enones, by preparation from chiral natural products via resolved synthetic intermediates, by asymmetric synthesis, by microbial or enzymatic techniques, etc. Racemic 4-hydroxy-2-cyclopentenone (±)-**70** is easily obtainable from furan derivatives or cyclopentadiene. *Clauson-Kaas* and *Limborg* et al. found that oxidative dimethoxylation[45a] of 2-methylfuran **69** with bromine and methanol, followed by treatment with a phosphate buffer (pH 7.4) afforded (±)-**70** in 55% overall yield (Scheme 22)[46].



61, X = I
62, X = Br
3
64, X = I
65, X = Br
66
67
68

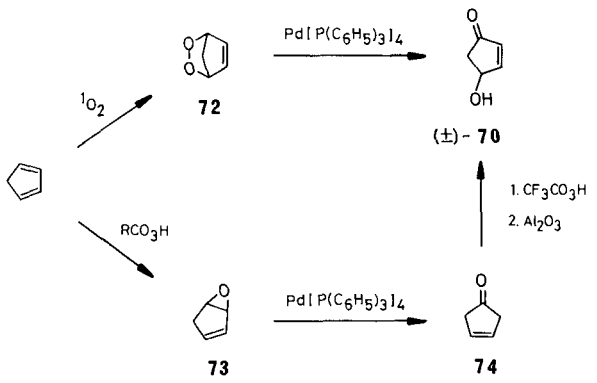
Scheme 21. Utility of the reduction with BINAL-H reagents (**3**, **67**) in the preparation of prostaglandin ω side-chains.



69
(±)-**70**
71

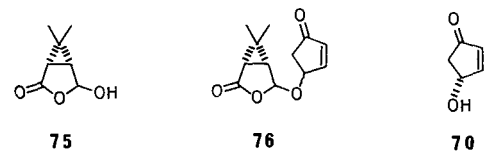
Scheme 22. Synthesis of 4-hydroxy-2-cyclopentenone (±)-**70** from furan derivatives.

The hydroxy ketone is also produced by simple acid-catalyzed rearrangement of 2-furfuryl alcohol **71**[47]. We found that regiospecific 1,4-oxygenation of cyclopentadiene leads to the same enone, where a palladium(0) complex plays an important role in the catalytic isomerization of strained oxygen-containing compounds (Scheme 23)[48]. When the 1,4-epidioxide **72**, formed by dye-sensitized photooxygenation of cyclopentadiene, was treated with 10 mol-% of tetrakis(triphenylphosphane)palladium(0) in dichloromethane, (±)-**70** was produced in 54% yield[48b]. On the other hand, treatment of cyclopentadiene epoxide **73** with this palladium complex in dichloromethane at 0 to 10°C gave exclusively 3-cyclopentenone **74** in 88% yield[48a].

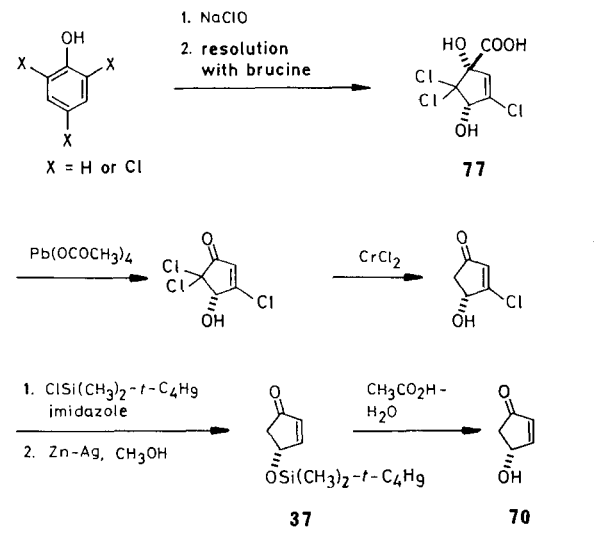


Scheme 23. Synthesis of 4-hydroxy-2-cyclopentenone (±)-**70** from cyclopentadiene.

This catalysis is very effective and the turnover number reaches 10^6! Further oxidation of **74** with trifluoroperacetic acid and treatment of the resulting epoxy ketone with alumina gave (±)-**70**. The hydroxy enone is a rather sensitive compound and hence the optical resolution is not easy by conventional methods. Fortunately, however, the bicyclic species **75**[49], derived from (1*S*,3*S*)-*trans*-chrysanthemic acid, proved to be an efficient resolving agent[50]. Pyridinium tosylate-catalyzed condensation of the racemic keto alcohol with **75** gave the diastereomeric adducts **76**, which could be easily separated on a silica gel column. Hydrolysis of the more polar isomer in a 1:2 mixture of dioxane and water at 70°C furnished the desired (*R*)-4-hydroxy-2-cyclopentenone **70**. The optical purity was greater than 97% and the overall yield was 88%.



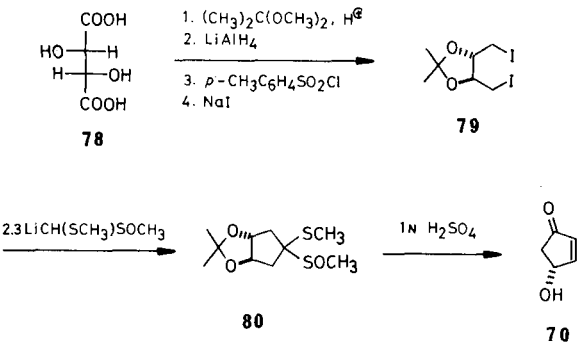
Gill and *Rickards* prepared **70** from phenol or 2,4,6-trichlorophenol as outlined in Scheme 24[18b,51]. This route



Scheme 24. Synthesis of (*R*)-4-hydroxy-2-cyclopentenone **70** from phenol derivatives.

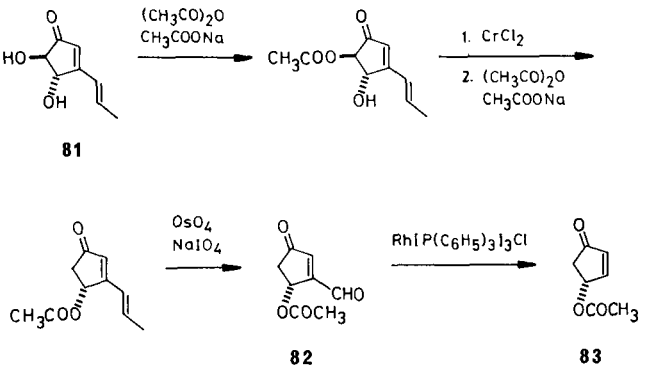
involves resolution of the hydroxy acid intermediate (±)-**77**[52] with brucine (37% yield, 74% of theory). The 1*S*,4*S* compound was transformed into the silyl protected hydroxy enone **37** in four steps in 56% overall yield. Hydrolysis of **37** gave optically pure free hydroxy ketone **70**.

Tsuchihashi et al. used unnatural D-tartaric acid **78** as a chiral pool for the synthesis of optically active **70** (Scheme 25)[53]. Using the known, four-step procedure[54], **78** was



Scheme 25. Synthesis of (*R*)-4-hydroxy-2-cyclopentenone **70** from D-tartaric acid.

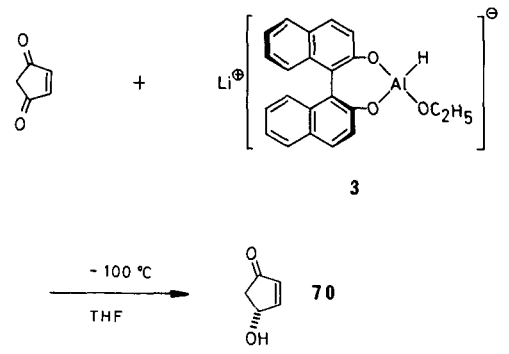
converted into the diiodide **79** in 42% yield. Base-induced condensation of **79** with methyl methylthiomethyl sulfoxide afforded **80**, which on subsequent acid-catalyzed hydrolysis gave the hydroxy enone **70** (85% optical purity) in 52.5% yield. As found by *Mitscher* et al.[55], naturally occurring terrein **81**, a metabolite of *Aspergillus fischerii*, can also serve as starting material.



Scheme 26. Synthesis of (*R*)-4-oxo-2-cyclopentenyl acetate **83** from terrein **81**.

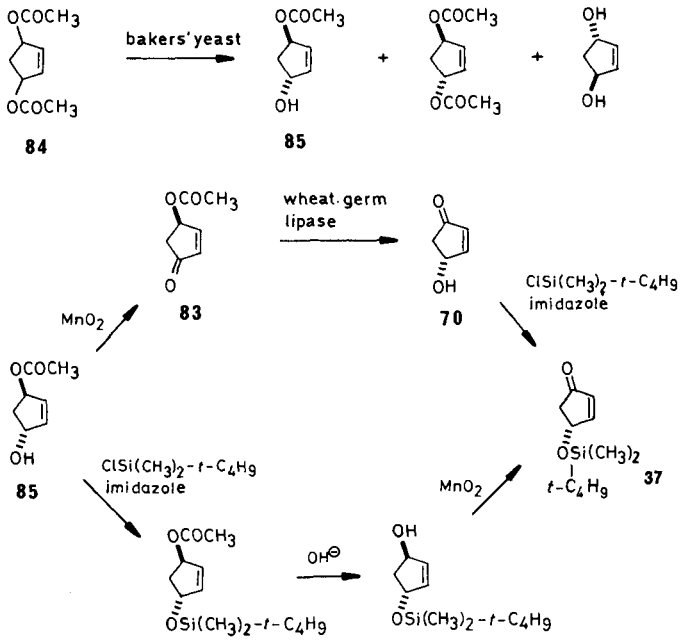
Scheme 26 illustrates the transformation of the highly functionalized chiral cyclopentenone into the protected hydroxy enone **83**. The olefinic side chain was removed by oxidative cleavage, giving the aldehyde **82**, followed by rhodium(I)-catalyzed decarbonylation (56%). The overall yield of the five-step synthesis was 33%. **83** was converted into **70** by enzymatic hydrolysis[57].

Asymmetric synthesis is also employable (Scheme 27); reduction of 4-cyclopentene-1,3-dione with (*S*)-BINAL-H reagent **3** in THF at −100°C afforded the hydroxy enone **70** in 94% *ee* (65% yield)[56,114d].



Scheme 27. Asymmetric synthesis of (*R*)-4-hydroxy-2-cyclopentenone **70**.

An enzymatic kinetic resolution technique was utilized by a Teijin research group (Scheme 28)[57]. When a stereoisomeric mixture of the 1,4-diacetate **84**, prepared from cyclopentadiene by bromination[58] and substitution with acetate, was hydrolyzed by bakers' yeast, the optically actife (3*R*,5*R*)-form of the half ester **85** (90% *ee*) was obtained in 3.2% yield. Oxidation of **85** with manganese dioxide (78%) and deacetylation by wheat germ lipase afforded the hydroxy enone **70** (90% optical purity) in 87% yield. Reaction of **70** with *tert*-butyldimethylsilyl chloride and imidazole furnished the protected cyclopentenone **37**. The same compound can also be obtained from **85** by silylation, hydrolysis, and oxidation (88% overall yield).

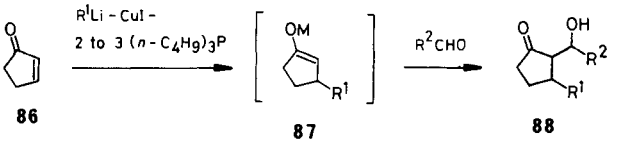


Scheme 28. Synthesis of (*R*)-4-hydroxy-2-cyclopentenone **70** using an enzymatic technique.

3.2. Double Vicinal CC-Coupling with α,β-Unsaturated Ketones

Having various procedures available for obtaining optically active building blocks, it was now necessary to develop an efficient method for assembling them. As described above (Section 2), the existing procedures for consecutive introduction of two side chains into 4-oxygenated 2-cyclopentenones are totally unsatisfactory. The main difficulty lies in the clean trapping of the organometallic-generated enolates with an α side-chain equivalent with preservation of the oxygen functionalities on C-4. Only very few electrophiles are capable of reacting with the non-equilibrated enolates in a desired manner[28].

Simple conjugate additions for the β-substitution of α,β-unsaturated ketones are usually carried out with the organocopper reagent in excess in order to ensure respectable results[26]. In reactions of the cuprates of type $LiCuR_2$ (Gilman reagents) one equivalent of the R group is inevitably wasted even in the ideal case. This becomes a severe disadvantage when the organic group is expensive or difficult to prepare. We considered, that the use of an excess of the ω side-chain equivalent in the key steps of a reaction such as the double vicinal CC-coupling of protected 4-hydroxy-2-cyclopentenones is unreasonable, not only from the economic but also from the chemical standpoint. The excess of organometallic compound makes the reaction system complicated[29] and thereby disturbs reaction between the enolate species and α side-chain electrophiles, resulting in the formation of complex mixtures[28]. On the other hand, if the nucleophilic delivery of the ω side chain is attained ideally by using only one equivalent of the reagent, the resulting enolate becomes the only strong nucleophile present in the reaction system and, therefore, it is anticipated that it will react cleanly with an equimolar amount of an α side-chain electrophile. In this context, we reinvestigated the existing procedures using 2-cyclopentenone **86** as a model substrate and found a simple, general solution to this problem[50,59]. First, we prepared the organocopper reagent from equimolar amounts of copper(I) iodide and organolithium compound and 2—3 equivalents of tri-*n*-butylphosphane. When such reagents were allowed to react with **86** (1 : 1 molar ratio) in ether or THF at low temperatures, the corresponding conjugate addition products were obtained in high yield. The requisite double vicinal CC-coupling is also possible in this way. As depicted in Scheme 29, the regiochemically defined enolate intermediate **87** could be trapped efficiently with one equivalent of an aldehyde as the aldol adduct **88**[50]. No α',β-condensation products associated with possible enolate equilibration were detected.

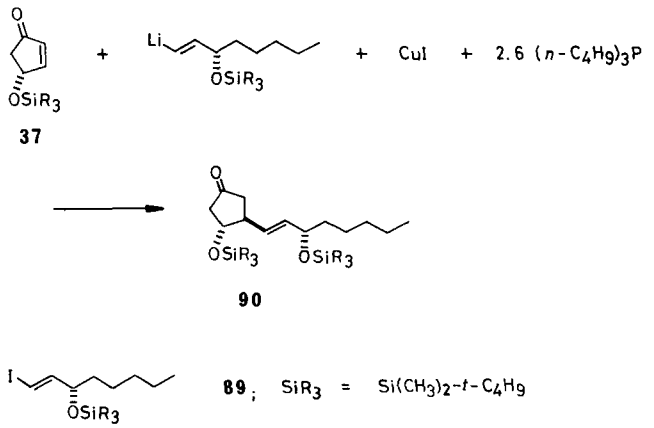


Scheme 29. Double vicinal CC-coupling of organocopper reagents with the model compound 2-cyclopentenone **86**. M = Li, Cu or Li + Cu; R^1 = *prim-*, *sec-*, *tert*-alkyl, -alkenyl etc.

3.3. Synthesis of Prostaglandins of Series 1

With an efficient method for consecutive nucleophilic/electrophilic double vicinal CC-coupling with enones, on the one hand, and diverse proven methods for obtaining

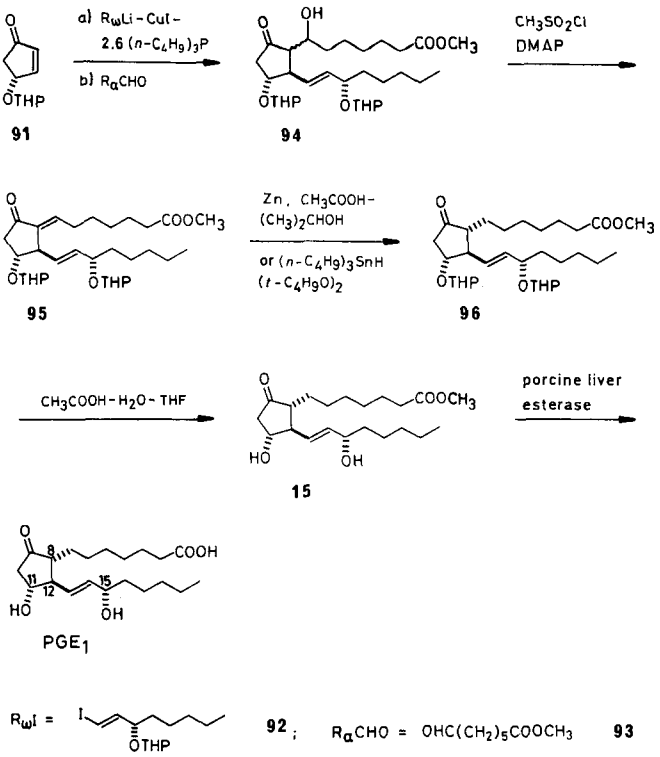
chiral building blocks, on the other, the three-component coupling process (see Scheme 12) held promise as a very straightforward entry to prostaglandins. First, we investigated the stereochemistry of the organocopper-mediated coupling of protected 4-hydroxy-2-cyclopentenones and the ω side-chain unit. The copper reagent was prepared by sequential treatment of the optically pure vinyl iodide **89** at −95 to −78°C with two equivalents of *tert*-butyllithium, one equivalent of copper(I) iodide, and 2.6 equivalents of tri-*n*-butylphosphane in ether. When this reagent was coupled to the (*R*)-4-siloxy enone **37** in THF at −78°C, as anticipated, a single *trans* adduct **90** was obtained after aqueous work-up (Scheme 30)[60]. Thus, the simple 4-oxygenated 2-cyclopentenone underwent high-yield conjugate addition with the natural (*E*)-vinylcopper reagent, whereby the C-3/C-4 *trans* relationship was established simply by steric interactions between the C-4 functionality and the entering organometallic reagent.



Scheme 30. Stereochemistry of the conjugate addition of an ω side-chain with organocopper reagents.

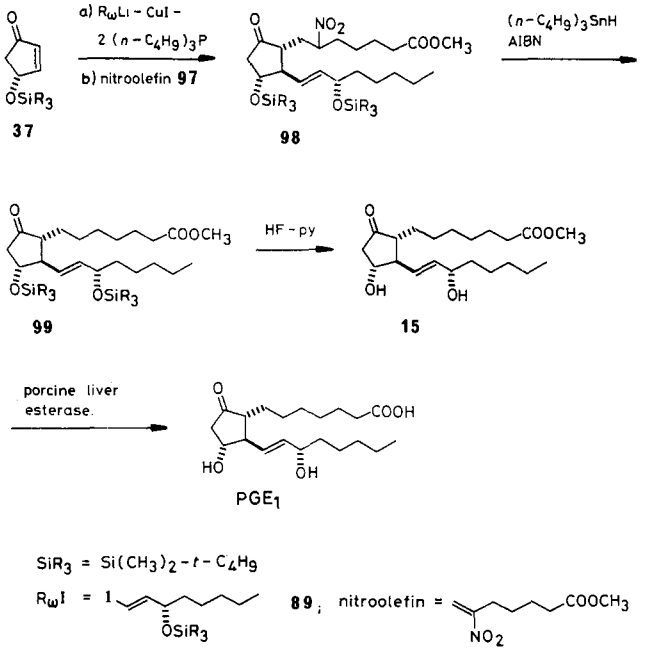
Scheme 31 outlines the convergent synthesis of PGE_1[50] which we have realized on this basis.

Our newly elaborated three-component coupling procedure using the enone **91**, the iodide **92** (as building block for the ω side-chain), and the aldehyde **93** (building block for the α side-chain) led to the aldol **94** as a mixture of diastereomers. The one-pot, direct construction of the functionalized prostaglandin skeleton was achieved in 83% yield[61]. Dehydration of **94** with methanesulfonyl chloride and 4-dimethylaminopyridine gave the enone **95** in 92% yield, which, on treatment with an excess of zinc dust in 2-propanol/acetic acid (95:5) gave the ketone **96** in 84% yield. Use of tri-*n*-butyltin hydride and di-*tert*-butyl peroxide increased the product yield to 90%. Removal of the tetrahydropyranyl protective groups in a 3:1:1 mixture of acetic acid, THF, and water afforded the PGE_1 methyl ester **15** in 92% yield. Finally, hydrolysis of the ester function by porcine liver esterase (86%)[62,63] completed the synthesis of natural PGE_1. This five-step synthesis of PGE_1 from the enone **91** was accomplished in 56% overall yield. Here, the absolute configuration at C-11 and C-15 are inherently determined at the stage of the starting materials, and the *trans* relationship of the ring-substituents is effected by the conjugate addition of the organocopper compound and subsequent operations.



Scheme 31. Convergent synthesis of PGE_1 (aldol route). DMAP = 4-dimethylaminopyridine.

Yet another short entry to PGE_1 has been opened up (Scheme 32)[63].

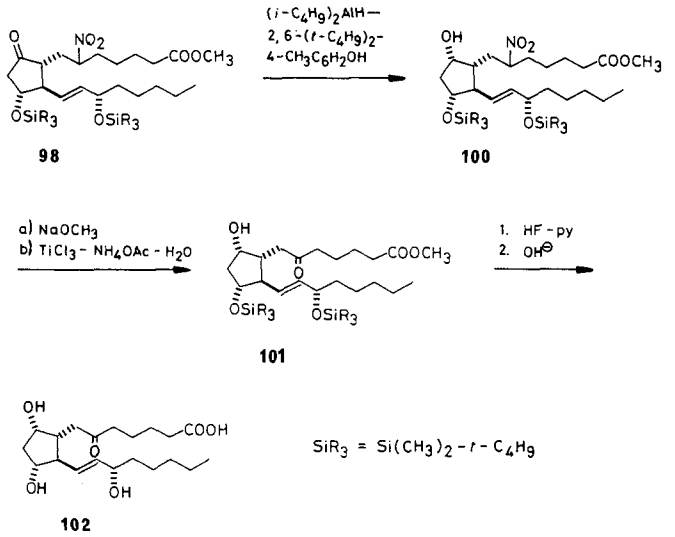


Scheme 32. Short synthesis of PGE_1 (nitro-intermediate route). AIBN = azobisisobutyronitrile.

The enolate intermediate generated by the reaction of the chiral enone **37** and the phosphane-complexed (*E*)-vinylcopper reagent, formed from **89**, underwent Michael

addition across the nitroolefin **97** in ether at −78 to −40 °C to give the adduct **98** in 58% yield. Removal of the 5-nitro group was effected by tri-*n*-butyltin hydride and azobisisobutyronitrile[64], giving **99** (30%); desilylation with hydrogen fluoride and pyridine in acetonitrile furnished the PGE_1 methyl ester **15** in 86% yield. Its enzymatic hydrolysis led to PGE_1[62]. Although this route must still be optimized, it nevertheless provides the shortest entry (only four steps from **37**) to natural PGE_1. Stereoselective reduction of **99** with the reagent formed from diisobutylaluminum hydride and a hindered phenol[10] affords **116**, which can be converted into $PGF_{1\alpha}$[77] (see Scheme 38).

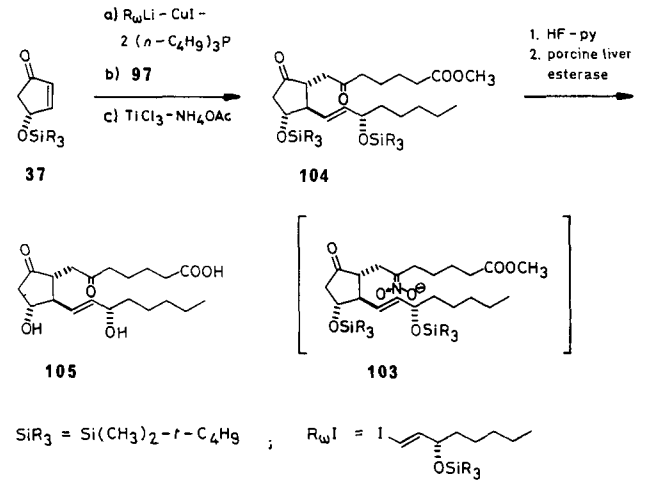
The stereoselective hydride reduction[10] of **98** gave the 9α-alcohol **100** as the major isomer (9α : 9β = 89 : 11, total yield 80%) (Scheme 33). The nitro compound was then



98 **100** **101** **102**

Scheme 33. Synthesis of 6-oxo-$PGF_{1\alpha}$ **102**.

converted into the 6-oxo derivative **101** (70% yield) under the Nef conditions[65]. Desilylation and saponification afforded 6-oxo-$PGF_{1\alpha}$ **102**, a degradation product of PGI_2, in 57% yield[66]. The utility of the nitroolefin trapping technique was further demonstrated by the short synthesis[67] of 6-oxo-PGE_1 **105**[68] (Scheme 34), which was previously

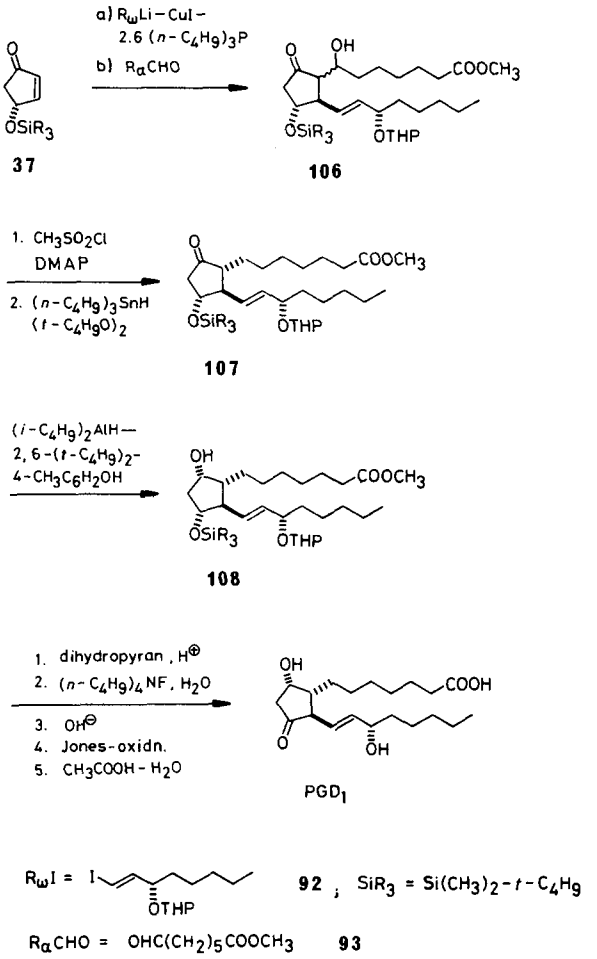


37 **104** **105** **103**

Scheme 34. Synthesis of 6-oxo-PGE_1 **105**.

prepared by a multistep synthesis via a PGI_2 derivative[69]. When the nitronate ion **103**, derived in situ by trapping of the enolate intermediate with the nitroolefin **97**, was treated with titanium(III) chloride/ammonium acetate[65], the ketonic product **104** was obtained in 76% yield. Deprotection (92%) and enzymatic hydrolysis (89%)[62] completed the three-step synthesis of 6-oxo-PGE_1 **105**.

Prostaglandins of the D series—like the analogues of the E series—have a β-hydroxycyclopentanone structure, but contain a hydroxy group at C-9 and a keto function at C-11. By choosing suitable protective groups in the synthetic building blocks, PGD_1 is, in principle, also accessible by the same pathway (Scheme 35)[70]. Silyl protection of 4-hydroxy-2-cyclopentenone and tetrahydropyranyl blocking



37 **106** **107** **108**

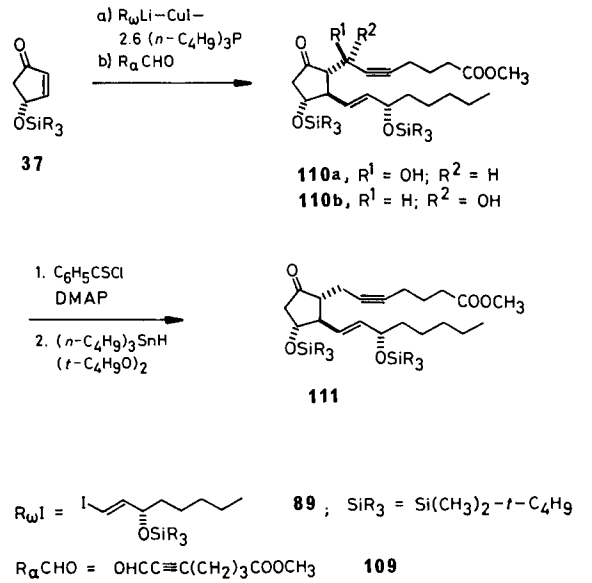
Scheme 35. Synthesis of PGD_1.

of the ω side-chain alcohol would appear to be among the most suitable. Thus, union of the cyclopentenone **37**, the ω side-chain **92**, and the α side-chain **93** by the tandem organocopper conjugate addition/aldol reaction gave rise to the prostanoic acid skeleton **106** (as a *threo/erythro* mixture of the aldols) in 70% yield. Dehydration of **106** by the standard procedure followed by reduction with tri-*n*-butyltin hydride gave the protected PGE_1 methyl ester **107** in 66% yield. The oxidation states of the C-9 and C-11 positions were easily rectified as follows: Reaction of **107** with *Yamamoto*'s phenol-modified diisobutylaluminum hydride reagent[10] resulted in the stereoselective reduction of

the 9-keto group (9α:9β = 88:12, 98% total yield); the main isomer of alcohol **108** was protected as tetrahydropyranyl ether (81%). Removal of the silyl group with tetra-*n*-butylammonium fluoride, alkaline hydrolysis of the ester, Jones oxidation of the 11-hydroxy function at −30°C, and deblocking of the tetrahydropyranyl groups furnished crystalline PGD_1 in 61% overall yield. The ester hydrolysis at the stage of 9,15-*O*-bis(tetrahydropyranyl)-$PGF_{1\alpha}$, rather than the final step, turned out to be more appropriate in view of the instability of PGD_1.

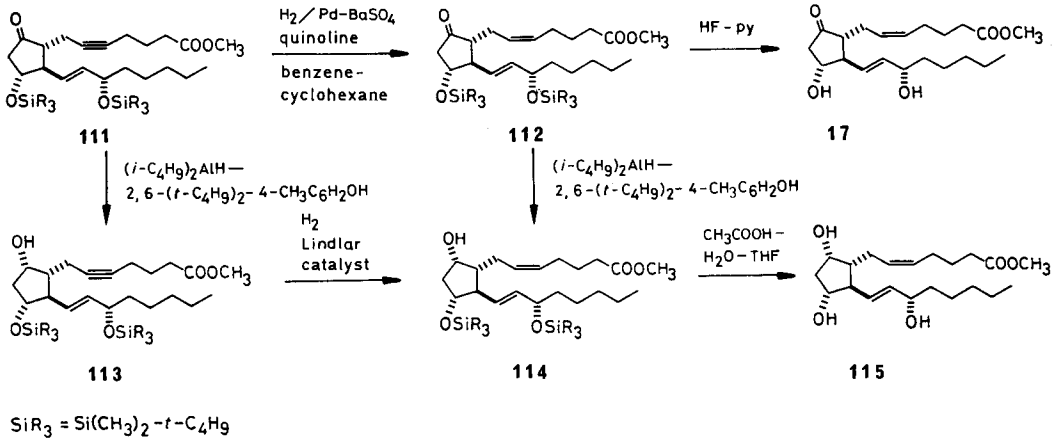
3.4. General Synthesis of Primary Prostaglandins

The conditions which an efficient prostaglandin synthesis must fulfill are wide generality and high flexibility. In the hope of opening a general route to primary prostaglandins, we chose as building block for the α side-chain methyl 6-formyl-5-hexynoate **109**, an acetylenic aldehyde which is readily obtainable by chain extension of propargyl tetrahydropyranyl ether[71] and *Swern* oxidation[72] of the corresponding alcohol. The tandem organocopper conjugate addition/aldol reaction was carried out with the cyclopentenone **37**, an (*E*)-alkenylcopper reagent derived from **89**, and the acetylenic aldehyde **109** in ether at −78°C to give the aldol adduct **110** (a 1:1 mixture of C-7 epimers)[73] (Scheme 36)[77]. The yield of the double vicinal CC-coupling is highly dependent on the structures of the building blocks, particularly the nature of the hydroxy protective groups, as well as the reaction and work-up conditions. The adduct **110** is obtainable in 83% yield if the conjugate addition is carried out in THF at −78°C and one equivalent of $BF_3 \cdot O(C_2H_5)_2$ is added prior to the reaction with the aldehyde **109**[60]. This procedure is quite reliable and reproducible. The 7-hydroxy group could not be removed by dehydration and reduction; however, the *Barton* method[78] proved successful. Thus, reaction of the aldols **110** with thiobenzoyl chloride and 4-dimethylaminopyridine afforded the thiobenzoate (71%), which upon heating at 50°C with tri-*n*-butyltin hydride in the presence of di-*tert*-butyl peroxide afforded a single deoxygenated compound **111** in 98% yield[79]. The smooth removal of the thiobenzoate moiety relies heavily on the presence of the 5,6-triple bond, which provides propargylic resonance stabilization to the radical intermediate. It is well known that simple β-ketoalkyl radicals undergo facile skeletal rearrangement via the tautomeric cyclopropyloxy radicals[80].



Scheme 36. Synthesis of the 5,6-dehydro-PGE_2 derivative **111**.

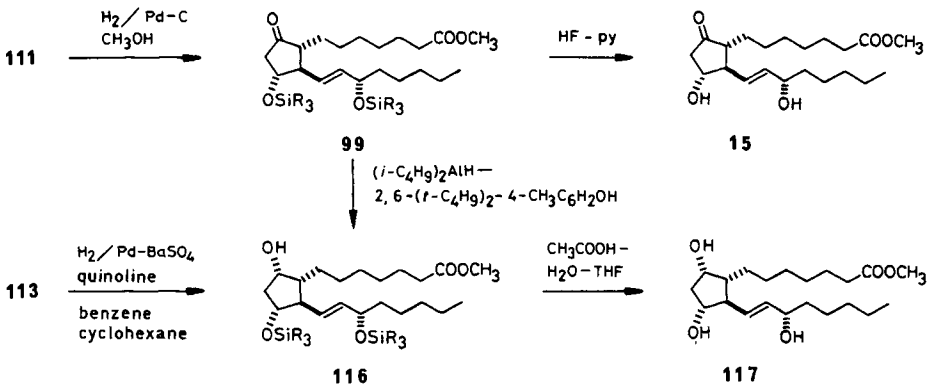
Clearly, the 5,6-dehydro-PGE_2 derivative **111** can serve as common intermediate for the synthesis of a variety of primary prostaglandins. Partial hydrogenation of the triple bond over 5% $Pd/BaSO_4$ catalyst in benzene/cyclohexane in the presence of quinoline led to **112** in 87% yield (Scheme 37). Removal of the silyl groups with hydrogen fluoride/pyridine gave the PGE_2 methyl ester **17** (98%), which could be converted into PGE_2 by an enzymatic technique[14c]. Reduction of the ketone **111** with the aforementioned phenol-modified diisobutylaluminum hydride reagent[10] in toluene at −25 to −20°C afforded the 9α-alcohol **113** with high stereoselectivity (α:β = 92:8) in 92% yield. **113** was also obtained (in 73% yield) from the thiobenzoate of the aldol **110** by stereoselective reduction with $NaBH_4$ (α:β = 9:1) and subsequent treatment with tri-*n*-butyltin hydride/di-*tert*-butyl peroxide. Catalytic hydrogenation of **113** over a Lindlar catalyst in benzene/cyclohexane with hydrogen at atmospheric pressure afforded **114** (81%). This compound was identical with the sample



Scheme 37. Synthesis of the PGE_2 methyl ester **17** and $PGF_{2\alpha}$ methyl ester **115**.

obtained in 87% yield by the stereoselective hydride reduction[10] of the PGE_2 derivative **112** (9α:9β = 91:9). Finally, deprotection of the disilyl derivative **114** with acetic acid/water/THF (10:3:1) furnished the $PGF_{2\alpha}$ methyl ester **115** (85%), whose ester group can be removed by alkaline hydrolysis.

Prostaglandins of the series 1 are also accessible from **111** and **113** by controlled reduction of the triple bond under conditions in which the CC double bond remains intact (Scheme 38)[77]. Thus, hydrogenation of **111** over 5% Pd/C in methanol to give **99** (71%) and subsequent desilylation with HF/pyridine gave the PGE_1 methyl ester **15** in 95% yield. Catalytic hydrogenation of **113** over 5% Pd/$BaSO_4$ in benzene/cyclohexane in the presence of quinoline afforded **116** (60%). Stereoselective reduction of **99** with diisobutylaluminum hydride/2,6-di-*tert*-butyl-4-methylphenol also gave predominantly the same alcohol (9α:9β = 91:9) in 76% yield. Deprotection of **116** under standard conditions furnished the $PGF_{1\alpha}$ methyl ester **117**.



SiR_3 = $Si(CH_3)_2$-*t*-C_4H_9

Scheme 38. Synthesis of PGE_1 methyl ester **15** and $PGF_{1\alpha}$ methyl ester **117** from the common intermediate **111**.

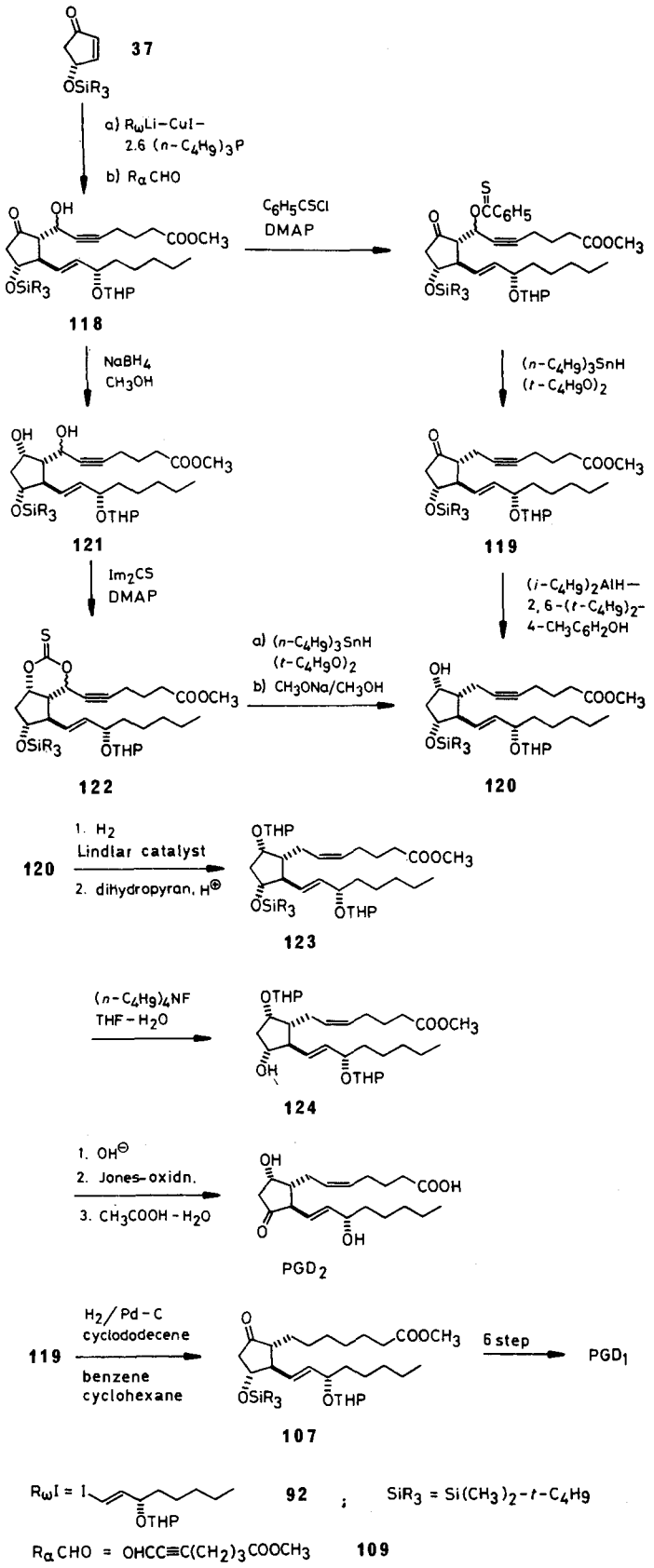
This strategy also allows the general synthesis of prostaglandins of type D, as illustrated in Scheme 39[70]. The aldol **118** (mixture of C-7 epimers) was obtained by double vicinal CC-coupling of the silylated hydroxycyclopentenone **37** with equimolar amounts of the tetrahydropyranyl-protected ω side-chain alcohol **92** and the acetylenic aldehyde **109** (yield 65%). Application of *Barton*'s procedure[78] to remove the 7-hydroxy group gave the deoxy compound **119** in ca. 66% yield. Reversal of the oxidation states of C-9 and C-11 was achieved in the above described manner. Reduction of **119** with excess diisobutylaluminum hydride/di-*tert*-butyl-4-methylphenol reagent[10] at −78 to −20 °C gave the 9α-alcohol **120** in 86% yield together with 8% of the 9β-isomer. **120** was also accessible by an alternative route from **118** via cyclic thiocarbonate intermediates **122**. When the more polar isomer of the aldol **118** was reduced with $NaBH_4$ in methanol at 0 °C, the corresponding 7,9-diol **121** was produced in a highly stereoselective fashion (9α:9β = 97.5:2.5, 77% yield). Formation of the cyclic thiocarbonate **122** with thiocarbonyl diimidazolide and 4-dimethylaminopyridine (92%) was followed by reduction with tri-*n*-butyltin hydride and alkaline hydrolysis of the ester function[81] to give the 7-deoxy product **120** (77%). The less polar isomer of the aldol **118** could also be converted into **120**, but the stereoselectivity of the hydride reduction was only moderate (9α:9β = 79:21). Partial hydrogenation of the acetylenic linkage of **120** was then effected over Lindlar catalyst in benzene/cyclohexane/cyclohexene with hydrogen at atmospheric pressure (96%); subsequent tetrahydropyranyl protection of the 9-hydroxy moiety (100%) afforded the suitably protected $PGF_{2\alpha}$ derivative **123**. Desilylation of **123** with tetra-*n*-butylammonium fluoride, to give **124** (95%), and subsequent saponification, Jones oxidation of the hydroxy carboxylic acid, and deblocking of the tetrahydropyranyl group completed the synthesis of PGD_2 (75%). Catalytic hydrogenation of **119** over 5% Pd/C in benzene/cyclohexane in the presence of cyclododecene afforded a PGD_1-precursor **107** in 68% yield (see also Scheme 35).

Prostaglandins of the A to C series can be derived from primary prostaglandins—hence, this method marks the realization of a new general synthesis of prostaglandins.

3.5. Synthesis of Prostacyclin and Related Compounds

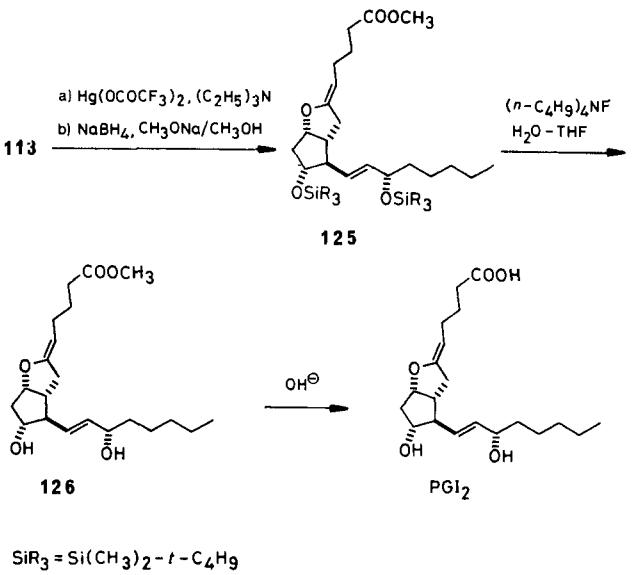
Prostacyclin (PGI_2), with its unique enol ether structure, has been synthesized in a roundabout way via $PGF_{2\alpha}$[13]. We found a simple *de novo* synthesis by way of the acetylenic intermediate **113**[82].

One may consider that intramolecular alkoxymercuration of 5-alkynols such as **113** in a 5-*exo-dig* manner[83] followed by reductive removal of the mercury moiety from the organometal intermediate counts among the most promising strategies for constructing a 2-alkylidenetetrahydrofuran structure. Actually, the efficiency of such a transformation is highly influenced by the substitution pattern of the substrates and the reaction conditions[84]; in some cases the reaction is quite complicated because of the concomitant side reactions such as double alkoxymercuration, acetal formation by solvent addition to the alkenyl ether intermediate, hydrolysis of the products during work-up, etc. Fortunately, we have found that the acetylenic alcohol



Scheme 39. Synthesis of prostaglandins D_1 and D_2.

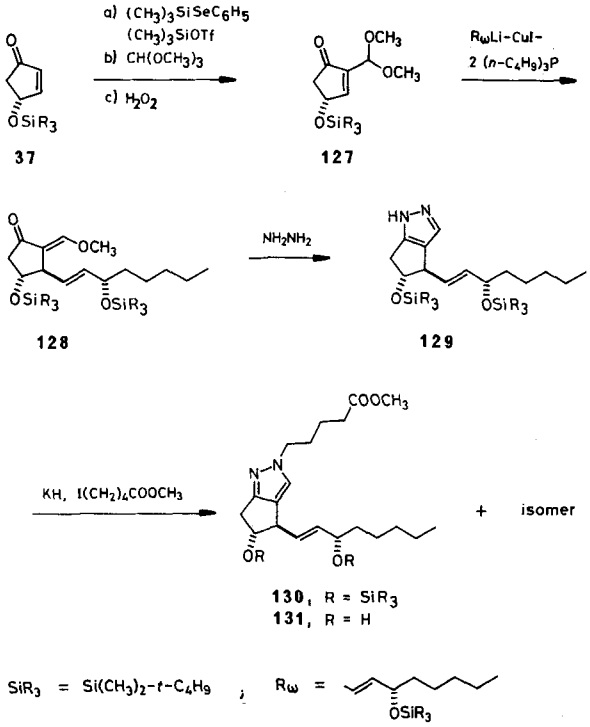
113 can be converted into a PGI_2 derivative **125** by sequential treatment with a mixture of a small excess of mercury(II) trifluoroacetate and triethylamine in THF at −78 °C and a 1 M methanolic sodium methoxide solution



Scheme 40. Synthesis of prostacyclin (PGI_2).

containing five equivalents of $NaBH_4$[82] (Scheme 40). After careful work-up and chromatography with added triethylamine, the cyclization product **125** (67% yield, 96% yield based on consumed starting material) and recovered **113** (30%) were obtained. The overall transformation appeared to proceed in a stereospecific manner, giving the (5*Z*)-isomer as sole product[85]. The intramolecular alkoxymercuration of the triple bond was accomplished stereospecifically in an *anti* fashion. Remarkably, the reductive demercuration of the resulting alkenylmercury trifluoroacetate with $NaBH_4$ in the protic medium occurred via a non-radical mechanism[86] with retention of the stereochemical integrity. This is in marked contrast with the reduction of alkylmercury compounds, which generates free alkyl radicals[87], and leads to stereorandom reactions. Deblocking of the silyl derivative **125** by tetra-*n*-butylammonium fluoride gave the PGI_2 methyl ester **126** (74%). Its alkaline hydrolysis leads to PGI_2[13]. Thus, PGI_2 is accessible in only seven steps from the chiral cyclopentenone **37**.

Prostacyclin, being the most potent natural inhibitor of blood platelet aggregation and a powerful vasodilator[1a, 1e], is recognized as one of the most significant compounds in the prostaglandin family. Unfortunately, however, it is exceedingly labile and is readily hydrolyzed to 6-oxo-$PGF_{1\alpha}$ **102** (half-life under physiological conditions only 5 min)[88]. One way of increasing the chemical stability is by replacing the alkylidenetetrahydrofuran skeleton by heteroaromatic rings; extensive efforts have been made in this direction[89]. We have synthesized a pyrazole-prostacyclin, as outlined in Scheme 41[90]. The optically pure siloxycyclopentenone **37** was first converted into the dimethoxymethyl derivative **127** in 79% yield by sequential treatment in dichloromethane with 1) one equivalent of phenylselenotrimethylsilane and a catalytic amount of trimethylsilyl triflate[91], 2) one equivalent of trimethyl orthoformate[92], 3) a small amount of pyridine, and 4) an excess of 30% hydrogen peroxide[93]. Subsequent conjugate addition in ether of an organocopper reagent prepared from equimolar amounts of copper(I) iodide, the lithium compound de-



37 127 128 129

130, R = SiR_3
131, R = H

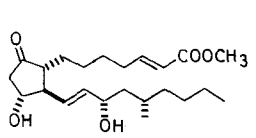
Scheme 41. Synthesis of the PGI_2 analogue **131**. Tf = trifluoromethanesulfonyl.

rived from the ω side-chain iodide **89**, and two equivalents of tri-*n*-butylphosphane gave the adduct **128** in 48% yield[49]. Ring closure was accomplished by reaction with excess hydrazine hydrate and the resulting pyrazole derivative **129** (84%) was alkylated with potassium hydride and methyl 5-iodopentanoate to give an approximately 1:1 mixture of **130** and its positional isomer (total yield 67%). Finally, deprotection of **130** with tetra-*n*-butylammonium fluoride completed the synthesis of **131** (77%). Although no significant biological properties of this compound have as yet been uncovered, such a method constitutes an attractive new way to a number of heteroaromatic prostacyclin analogues in optically active form.

3.6. Some Physiologically Interesting Analogues

The three-component coupling process enables the synthesis of a wide range of physiologically significant analogues by choosing appropriately modified side-chain units.

First, this direct method provides a rapid entry to some prostaglandin analogues which have been prepared by the existing procedures and are presently undergoing clinical trials. A typical example is provided by the efficient synthesis[94] of (17*S*)-17,20-dimethyl-Δ^2-PGE_1 **132**[95], a powerful antithrombotic agent[95b], starting from the optically active cyclopentenone **37**, the (3*S*,5*S*)-iodovinyl alcohol **136**, and (*E*)-methyl 6-formyl-2-hexenoate. Scheme 42[67,96] illustrates the access to **136**, the optically active building block of the ω side chain (*ee* > 99%), starting from racemic 3-butanolide **133**[97].



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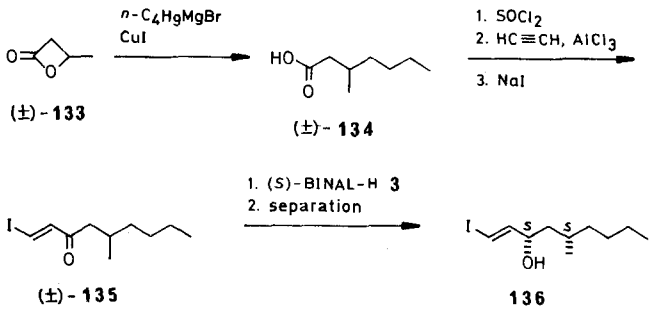
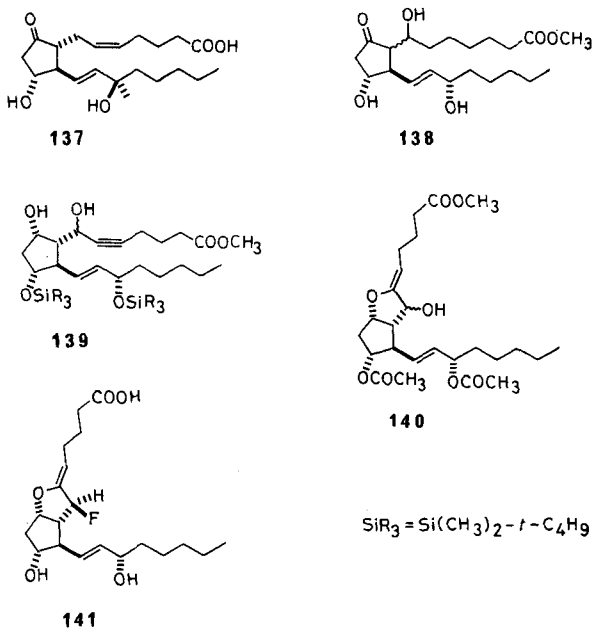


(±)-133 (±)-134 (±)-135 136

Scheme 42. Synthesis of optically active building blocks for ω side chains.

The absolute configuration of **136** was determined by the exciton chirality method using the derived *p*-bromobenzoate[74]. The alcohol **136** can also be prepared by a sequence involving an asymmetric synthesis[67,98].

(15*R*)-15-Methyl-PGE_2 **137** is known as a unique antiulcer drug[99]. This compound could also be conveniently prepared by the aldol route[94,100].



137 138 139 140

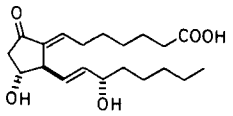
$SiR_3 = Si(CH_3)_2$-t-C_4H_9

141

The functional groups on C-7 or C-6 of the three-component linked products not only serve as triggers of further chemical transformations but also of biological activities. For instance, the readily accessible 7-hydroxy-PGE_1 **138**[101] was found to be a potent inhibitor of platelet aggregation[102]. The acetylenic diol **139**[76] is convertible into the 7-hydroxy-PGI_2 derivative **140** by the alkoxymercuration technique[76]. Treatment of a mixture of the C-7 epimers with diethylaminosulfur trifluoride followed by deprotection and saponification gave stereoselectively (7*S*)-fluoro-PGI_2 **141**[76,103a] as the sodium salt. Such a 7-fluoro-PGI_2 derivative enjoys greater stability than PGI_2 under physiological conditions[103]. The inhibitory activity of **141** on rabbit platelet aggregation induced by ADP is only one tenth of that of the natural PGI_2, but both are equally po-

tent with regard to human platelets. **141** possesses lower hypotensive activity than PGI_2 and hence is a candidate for useful anti-platelet agents[103a].

Recently, intense interest has been attached to the anti-neoplastic activities of primary and other prostaglandins such as PGA_2, PGD_2, and PGJ_2 (9-deoxy-Δ^9-PGD_2)[104]. Δ^7-PG derivatives[105] obtained by dehydration of the aldol intermediates are noteworthy in this respect. Many analogues of this type, **142**—**145**, as well as clavulone[106] (or claviridenone[107]) **146** isolated from *Clavularia viridis* were



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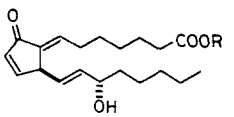
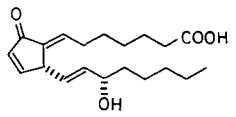


143, R = CH_3
144, R = H



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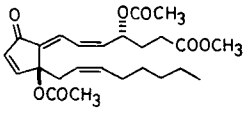
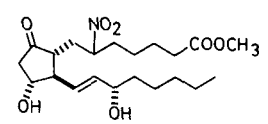


146

found to exhibit profound antineoplastic effects *in vitro* and *in vivo*[108]. For example, Δ^7-PGA_1 **144** inhibited the growth of L1210 tumor cells at concentrations of 0.2—0.4 μg/mL (IC_{50}) and suppressed the growth of Ehrlich ascites tumors at doses of 20 mg/kg (i.p. administration)[108b]. These derivatives are far more active than ordinary prostaglandin derivatives. Remarkably, 12-*epi*-Δ^7-PGA_1 **145** exhibits a similar activity, which indicates the possible separation of anti-neoplastic effects from the undesired prostaglandin activities.

The tandem organocopper conjugate addition/nitroolefin Michael reaction is also useful. The 6-nitro-PGE_1 methyl ester **147** thus obtained has a more selective hypotensive activity than PGE_1[94,109]. 15-Deoxy-16-hydroxy-16-methyl-PGE_1 methyl ester **148**, an anti-ulcer agent which was developed by a Searle group[110], is accessible from the



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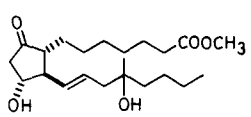

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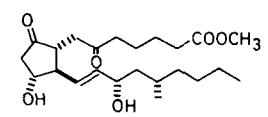

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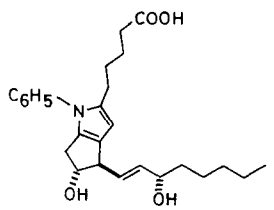

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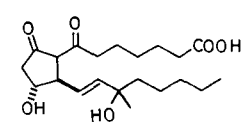


151

corresponding 6-nitro derivative by reduction with tri-*n*-butyltin hydride[63,94]. Ono and Upjohn have jointly been developing the 6-oxo-PGE_1 derivative **149**[69] as an anti-ulcer agent possessing cytoprotective properties. This three-component coupling process combined with the Nef reaction provides a two-step entry to this compound from **37**, **97**, and **136**[67]. Furthermore, a pyrrole derivative **150**, known as a leukotriene antagonist and an inhibitor of the leukotriene biosynthesis[111], is also accessible from **104** by a simple treatment with aniline followed by deprotection and saponification[94].

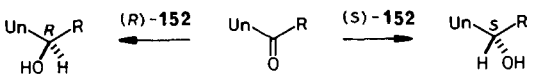
The 15-methyl-7-oxo-PGE_1 derivative **151** could be prepared quickly via the route described here using an acid chloride as the α side-chain unit[34]. This analogue[112] exhibits double the anti-ulcer activity of PGE_2 on oral administration, but, on the other hand, has a weaker diarrhea-inducing effect. **151** is relatively inert in terms of smooth muscle contraction, and is 100 times less potent than PGE_2 and $PGF_{2\alpha}$.

4. New Methods in Prostaglandin Synthesis

The realization of the new convergent synthesis of prostaglandins relies heavily on the discovery of versatile synthetic methodologies[113]. Some novel methods elaborated in our laboratories are described below.

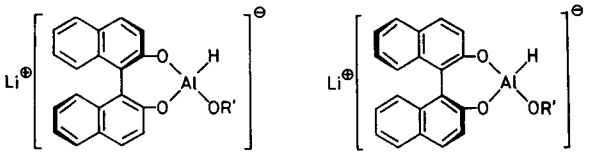
4.1. Enantioselective Reduction of Prochiral Carbonyl Compounds

A new chiral aluminum hydride agent, abbreviated as BINAL-H [(*R*)- or (*S*)-**152** (empirical form), cf. also **3** and **67**], was devised by modification of $LiAlH_4$ with equimolar amounts of optically pure 1,1'-bi-2-naphthol and a lower alcohol, R'OH[114]. This hydride reagent containing an axially dissymmetric auxiliary of C_2 chirality exhibits exceptionally high chiral recognition ability[115,116] in the reaction with prochiral unsaturated carbonyl compounds, giving the alcohols in high optical purity[9a,56]. As shown in Table 1, this reducing agent can be applied to a wide range of structurally diverse unsaturated carbonyl compounds such as aromatic ketones[114a,c], alkynyl ketones[42,114d], alkenyl ketones[9,56,114d], and aldehydes[114b,d] as well as dienones[114d]. Either of the enantiomers is obtainable with equal ease by appropriate choice of handedness of the auxiliary binaphthol ligand. The chiral ligands can be recovered from the reaction mixtures in reusable form. Asymmetric reductions of this kind are not only extremely useful in prostaglandin syntheses[9,56,114d], but are also of general utility, as has been substantiated by the effective stereocontrolled syntheses of insect pheromones[42,114d], chiral primary terpene alcohols[114b,d], styrene oxide[114d], steroid side chains[117], etc.



Un = phenyl, CH=CHR, C≡CR etc.
R = alkyl, H

Scheme 43. Orientation in the reduction with BINAL-H **152** (see Table 1).



(*R*) - **152**

(*S*) - **152**

Table 1. Asymmetric reduction of carbonyl compounds with BINAL-H reagents (cf. **152**) [a].

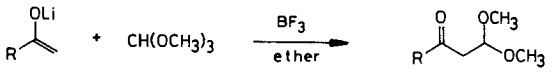
Carbonyl compound	**152**	Product		
		Yield [%]	*ee* [%]	Confign.
Aromatic ketones				
Acetophenone	*R*	61	95	*R*
Propiophenone	*S*	62	98	*S*
Butyrophenone	*S*	92	100	*S*
Valerophenone	*S*	64	100	*S*
Isobutyrophenone	*S*	68	71	*S*
Pivalophenone	*R*	80 [b]	44	*R*
α-Tetralone	*R*	91	74	*R*
α-Bromoacetophenone	*R*	97 [c]	95 [c]	*S*
Alkynyl ketones [d]				
1-Octyn-3-one	*S*	87	84	*S*
1-Undecyn-3-one	*S*	80	96	*S*
1-Tetradecyn-3-one	*S*	90	92	*S*
4-Methyl-1-pentyn-3-one	*S*	84	57	*S*
3-Octyn-2-one	*R*	79	84	*R*
7-Dodecyn-6-one	*S*	85	90	*S*
Methyl 4-oxo-5-tetradecynoate	*R*	80	84	*R*
Methyl 4-oxo-2-dodecynoate	*S*	80	87	*S*
Alkenyl ketones				
(*E*)-1-Cyclopentyl-1-octen-3-one	*R*	91	92	*R*
(*E*)-3-Octen-2-one	*R*	74	79	*R*
(*E*)-7-Dodecen-6-one	*R*	91	91	*R*
(*E*)-1-Iodo-1-octen-3-one	*S*	95	97	*S*
(*E*)-1-Bromo-1-octen-3-one	*S*	96	96	*S*
4-Cyclopenten-1,3-dione	*S*	65	94	*R*
Methyl 7-(3,5-dioxo-1-cyclopentenyl)heptanoate	*R*	26 [e]	81	*S*
(1*S*,5*R*,6*R*,7*R*)-7-Acetoxy-6-[(*E*)-3-oxo-1-octenyl]-2-oxabicyclo[3.3.0]octan-3-one	*S*	95	99.4 : 0.6 [f]	*S*
(1*S*,5*R*,6*R*,7*R*)-7-(Tetrahydro-2-pyranyloxy)-6-[(*E*)-3-oxo-1-octenyl]-2-oxabicyclo[3.3.0]octan-3-one	*S*	96	99.5 : 0.5 [f]	*S*
(1*S*,5*R*,6*R*,7*R*)-7-Hydroxy-6-[(*E*)-3-oxo-1-octenyl]-2-oxabicyclo[3.3.0]octan-3-one	*S*	97 [g]	100 : 0 [f]	*S*
(5*Z*,13*E*)-9α,11α-Bis(tetrahydro-2-pyranyloxy)-15-oxoprosta-5,13-dienoic acid methyl ester	*S*	88 [h]	100 : 0 [f]	*S*
β-Ionone	*S*	87	100	*S*
Dialkyl ketones				
2-Octanone	*R*	67	24	*S*
Benzyl methyl ketone	*S*	74	13	*S*
Deuterium labeled aldehydes				
[1D]Geranial	*S*	91	84	*S*
[1D]Neral	*S*	90	72	*S*
[1D](*E*,*E*)-Farnesal	*R*	91	88	*R*
[1D](*E*,*Z*)-Farnesal	*R*	93	82	*R*
[α-D]Benzaldehyde	*R*	100	87	*R*

[a] Prepared by successive mixing of lithium aluminium hydride with equimolar amounts of a simple acohol, usually ethanol, and (*R*)-or (*S*)-1,1′-bi-2-napthol in THF. Usually, reduction was conducted at −100 to −78 °C using 2–3 equivalents of BINAL-H. [b] Reaction at −100 °C to room temperature. [c] Value for styrene oxide formed on treatment with aquous NaOH. [d] Reduction with methanol-modified BINAL-H. [e] (*S*)-(+)-Methyl 7-(3-hydroxy-5-oxo-1-cyclopentenyl)heptanoate. [f] (15*S*)/(15*R*) (PG numbering) diastereomeric ratio. [g] Conversion was 43%. [h] Conversion was 63%.

From a mechanistic point of view, the empirical rule given in Scheme 43, which enables prediction of the configuration of the product in the reaction of BINAL-H **152** with simple substrates, is highly interesting: aryl, alkenyl, and alkynyl groups exert approximately the same directing influence in the creation of a new asymmetric center. This suggests that the BINAL-H reagents differentiate the saturated and unsaturated groups attached to the carbonyl function primarily by the difference in the electronic properties rather than the relative bulkiness[9, 56, 114c].

4.2. α-Dialkoxymethylation of Preformed Enolates

A formyl group-equivalent can be introduced into ketones in a regiocontrolled manner under mild conditions[118]. Preformed lithium enolates[119] react with an equimolar amount of trimethyl orthoformate at −78 °C in the presence of boron trifluoride to give the corresponding dimethoxymethylated ketones in good yields (Scheme 44,



Scheme 44. α-Dialkoxymethylation of enolates.

Table 2. Dimethoxymethylation of lithium enolates [a].

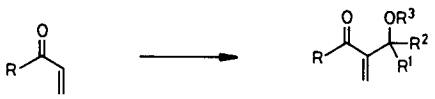
Enolate precursor	Yield [%] (*cis* : *trans*)
Acetophenone	84
Cyclopentanone	80
Cyclohexanone	87
4-*tert*-Butylcyclohexanone	72 (50 : 50)
4-Methylcyclohexanone [b]	79 (28 : 72)
2-Methylcyclohexanone [c]	68

[a] All reactions were conducted using equimolar amounts of trimethyl orthoformate and $BF_3 \cdot O(C_2H_5)_2$ in ether (1 h at −78 °C). [b] Less substituted enolate. [c] More substituted enolate.

Table 2). In this reaction, only mono-dimethoxymethylation takes place. The regiochemistry is defined at the stage of the lithium enolate. The stereochemistry at the α-position to the carbonyl group is kinetically controlled; the products do not undergo epimerization under the reaction conditions. This condensation is applicable to fully substituted enolates; with the conventional ketone formylation, using formates and sodium alkoxides, this is not possible, since it relies on the high stability of the resulting β-dicarbonyl compounds[120].

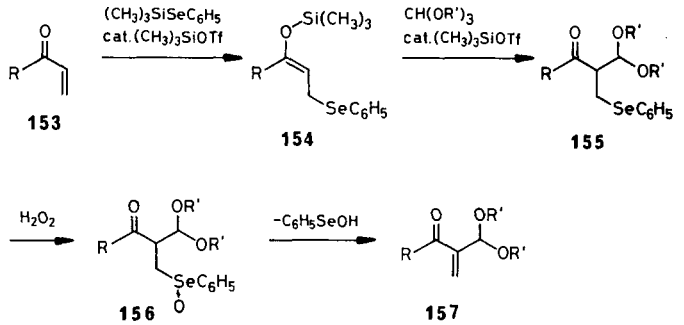
4.3. α-Alkoxyalkylation of α,β-Unsaturated Ketones

Although α-functionalized α,β-unsaturated ketones are versatile intermediates, direct introduction of substituents into the sp^2-hybridized α-position of enones is not an easy task[121]. We found a convenient procedure for converting cyclic or acyclic α,β-unsaturated ketones into α-alkoxyalkyl or -dialkoxyalkyl enones (Scheme 45)[122].



Scheme 45. α-Alkoxyalkylation of α,β-unsaturated ketones.

As shown in Scheme 46, conjugate addition of phenyl trimethylsilyl selenide to an enone substrate **153** generates the regiochemically defined silyl enol ether **154**[123], which in turn is condensed with a trialkyl orthoformate (or acetal)[91,92] to give the vicinally functionalized ketone **155**. Trimethylsilyl triflate serves as catalyst. Oxidative removal of the phenylseleno function by hydrogen peroxide[93] leads to the desired alkylation product (**155** → **156** → **157**). All the operations are accomplishable in dichloromethane in one pot without isolation of the intermediates, **154**—**156** (Scheme 46, Table 3). Trimethylsilyl triflate appears to



153 154 155 156 157

Scheme 46. Dialkoxymethylation of enones as a one-pot reaction.

Table 3. α-Alkoxyalkylation of α,β-unsaturated ketones [a].

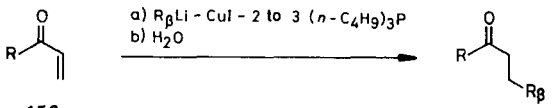
Enone	Acetal or orthoester	Product	Yield [%]
Methyl vinyl ketone	Benzaldehyde-dimethyl acetal	3-(α-Methoxybenzyl)-3-buten-2-one	57
Methyl vinyl ketone	Triethyl orthoformate	3-(Diethoxymethyl)-3-buten-2-one	53
2-Cyclopentenone	Trimethyl orthoformate	2-(Dimethoxymethyl)-2-cyclopentenone	58
2-Cyclohexenone	Benzaldehyde dimethyl acetal	2-(α-Methoxybenzyl)-2-cyclohexenone	75
2-Cyclohexenone	Acetophenone dimethyl acetal	2-(α-Methoxy-α-methylbenzyl)-2-cyclohexenone	30
2-Cyclohexenone	Cinnmaldehyde dimethyl acetal	2-(1-Methoxy-3-phenyl-2-propenyl)-2-cyclohexenone	83
2-Cyclohexenone	Triethyl orthoformate	2-(Diethoxymethyl)-2-cyclohexenone	76

[a] Usually, reaction of phenyl(trimethylsilyl) selenide and an enone (1 : 1 mol ratio) was conducted in dichloromethane in the presence of a catalytic amount (2–2.5 mol%) of trimethylsilyl triflate at −78 °C for 30 min. Reaction of the resulting silyl enol ether and an acetal or orthoester was performed at −50 to −20 °C for 0.5 to 1 h. Subsequent removal of the phenylseleno group was achieved by oxidation (30% H_2O_2, 0 °C) followed by heating of the system (15–40 °C).

play a unique role in such transformations[91]. The reaction conditions are mild enough for prostaglandin syntheses[90] which involve chemically and optically labile 4-oxygenated 2-cyclopentenones.

4.4. Conjugate Addition of Organocopper Compounds to α,β-Unsaturated Ketones

An effective method for the nucleophilic transfer of organic moieties to conjugate enones is of crucial importance in prostaglandin synthesis. In place of the classical Kharasch procedure using Grignard reagents and copper salt catalysts, many modern organic syntheses make use of lithium cuprates of the type $LiCuR_2$ (Gilman reagents) because of the higher efficiency, increased selectivity, and reproducibility[26]. Mixed cuprates of type LiCuRR' (R' = C≡C-*n*-C_3H_7[33], C≡CC$(CH_3)_3$[124], C$(CH_3)_3$[125], CN[126], OC$(CH_3)_3$[29a], OC_6H_5[29a], SC_6H_5[29a], PR_2[127] etc.) or higher-order cuprates, $Li_2Cu(CN)R_2$[128], may be used for this operation. The rationale described in Section 3.2 prompted us to search for a procedure which effects a smooth reaction using a minimum amount of organometallic reagent and, as a consequence, use of the organocopper reagents derived from copper(I) iodide, organolithium compounds, and tri-*n*-butylphosphane (molar ratio 1 : 1 : 2—3) turned out to be among the best[59]. Hexamethylphosphoric triamide is also usable as the phosphorus auxiliary[59]. The reaction proceeds smoothly with a wide variety of conjugated enones **153** in ether (yellow solution) or THF (heterogeneous) at −78 to −40 °C and leads, after aqueous work-up, to the β-substituted ketones **158** in high yields (Scheme 47, Table 4). This method is economical



153 158

Scheme 47. Conjugate addition of phosphane-complexed organocopper reagents to enones.

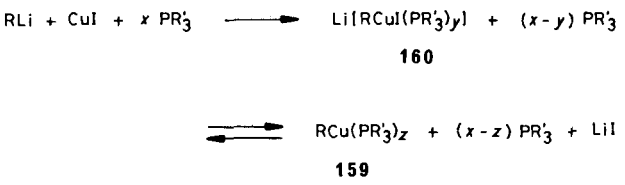
Table 4. Conjugate addition of organocopper compounds to enones [a].

Enone	Entering group	Yield [%]
(*E*)-5-Methyl-3-hexen-2-one	*n*-Butyl	94
(*E*)-5-Methyl-3-hexen-2-one	Isopropyl	95
(*E*)-5-Methyl-3-hexen-2-one	*tert*-Butyl	86
(*E*)-5-Methyl-3-hexen-2-one	Phenyl	84
4-Methyl-3-penten-2-one	*n*-Butyl	88 [b]
4-Methyl-3-penten-2-one	Isopropyl	99 [b]
4-Methyl-3-penten-2-one	Phenyl	70 [b]
4-Methyl-3-penten-2-one	Isopropenyl	66
2-Cyclopentenone	Methyl	73
2-Cyclopentenone	*n*-Butyl	98 [c]
2-Cyclopentenone	Isopropyl	90
2-Cyclopentenone	*tert*-Butyl	73
2-Cyclopentenone	Isopropenyl	98
2-Cyclopentenone	[d]	84 [c]
2-Cyclohexenone	Methyl	95 [b]
2-Cyclohexenone	*n*-Butyl	100
2-Cyclohexenone	Isopropyl	94
2-Cyclohexenone	*tert*-Butyl	91
2-Cyclohexenone	Isopropenyl	100
2-Cyclohexenone	[d]	75
3,5,5-Trimethyl-2-cyclohexenone	Methyl	28
3,5,5-Trimethyl-2-cyclohexenone	*n*-Butyl	100 [e]
3,5,5-Trimethyl-2-cyclohexenone	Isopropyl	100 [b, f]
3,5,5-Trimethyl-2-cyclohexenone	Isopropenyl	100

[a] Unless otherwise stated, reaction was carried out using a reagent prepared in situ by mixing copper(I) iodide, an organolithium compound, and tri-*n*-butylphosphane in the molar ratio 1 : 1 : 2–3 in ether (−78 °C for 0.5–1 h and then −40 °C, for 1–3 h). [b] Reaction at 0 °C for 5–10 min. [c] THF was used as solvent. [d] (*E*)-3-(2-Tetrahydropyranyloxy)-1-octenyl. [e] Yield based on the consumed sustrate. Conversion was 86%. [f] Yield based on the consumed enone. Conversion was 44%.

(enone/LiR = 1 : 1 to 1.25), can be applied to various sp^2- and sp^3-hybridized entering groups (methyl and primary, secondary, and tertiary alkyl), and compares well with the

existing reactions. The actual reaction system consists of a complex mixture of equilibrating species, as illustrated in Scheme 48. The organic group may be transferred to the lithium cation-coordinated enone substrates from the neutral organocopper complex **159** or from the anionic species **160**[129]. This still remains unclear.



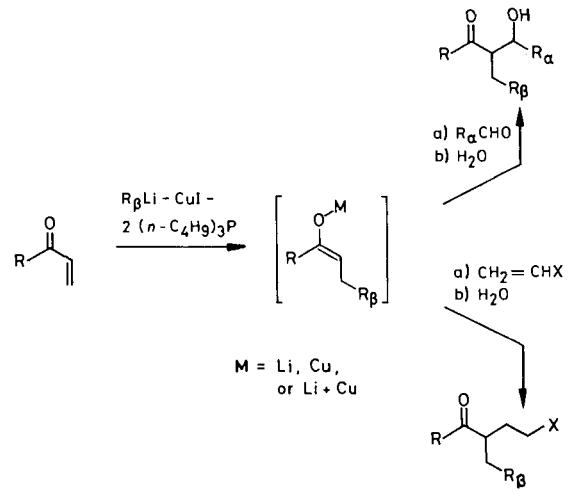
Scheme 48. Equilibration of organocopper species.

4.5. Double Vicinal CC-Coupling with Enones

4.5.1. Trapping Reactions of the Enolates Generated by Organocopper Compounds

Reactions of the enolates formed from enones and the phosphane-complexed organocopper reagents are easier to control than the reactions of such enolates generated from cuprates[29b, c, 130]. In fact, the regiochemically-defined enolates are capable of being trapped cleanly with aldehydes to give the corresponding aldol adducts (see Section 3.2 and Scheme 29)[50]. The three-component coupling process (Scheme 49, Table 5) is quite generally applicable. The enone : organolithium reagent (as precursor of the organocopper component) : aldehyde ratio is usually 1 : 1 : 1. Aliphatic aldehydes as trapping agents produce a single aldol adduct, whereas aromatic or α,β-unsaturated aldehydes give rise to a mixture of diastereomeric aldols (*threo* and *erythro*)[131].

The enolate intermediates undergo regiospecific Michael addition to nitroolefins (cf. Section 3.3)[63] and α,β-unsaturated ketones to give 2,3-disubstituted ketones (Scheme 49). The latter reaction has been used in the synthesis of steroids[132].



Scheme 49. Three-component coupling of enone, organocopper reagent, and electrophile. X = electron-withdrawing group.

Table 5. Double vicinal CC-coupling with α,β-unsaturated ketones via an organocupper/aldehyde joining process [a]. $R_\beta = n$-butyl.

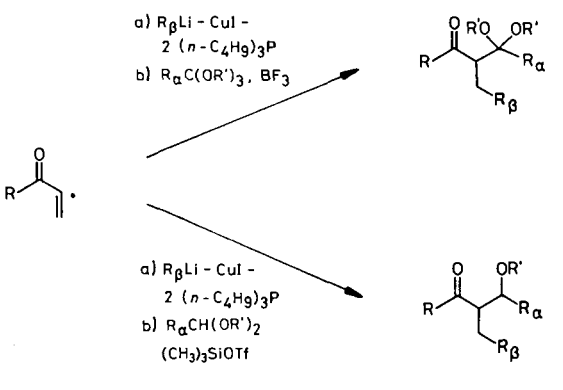
Enone	Aldehyde R_α–CHO	Aldol Yield [%]
2-Cyclohexenone	Formaldehyde [b]	60
2-Cyclohexenone	Acetoacetaldehyde	91
2-Cyclohexenone	(*E*)-Cinnamaldehyde	92 [c]
2-Cyclohexenone	Butanal	88 [d]
2-Cyclohexenone	2-Methylpropanal	94 [d, e]
2-Cyclohexenone	Benzaldehyde	85 [c]
2-Cyclopentenone	Butanal	98 [d]
2-Cyclopentenone	2-Methylpropanal	93 [d]
2-Cyclopentenone	2,2-Dimethylpropanal	71 [d]
2-Cyclopentenone	Benzaldehyde	91 [c]
2-Cyclopentenone	(*E*)-Cinnamaldehyde	94 [c]
2-Cyclopentenone	2-Hexynal	72 [c]

[a] The organocuprate-phosphane complex was prepared in situ by mixing copper(I) iodide, *n*-butyllithium, and tri-*n*-butylphosphane in the molar ratio 1 : 1 : 2 in ether. The conjugate addition was conducted at −40 to −70°C. Enolate trapping was carried out at −78°C for 5–60 min. [b] Introduced with an argon stream after cracking of paraformaldehyde. [c] A mixture of stereoisomeres. [d] A single isomer. [e] (2*R**,3*R**)-3-Butyl-2-((1*R**)-1-hydroxy-2-methylpropyl)cyclohexanone. This structure was determined by X-ray structure analysis of its *p*-bromobenzoate.

4.5.2. Trapping Reactions of the Enolates with Orthoesters or Acetals

Enolates formed from an enone by conjugate addition of an organocopper compound in stoichiometric amounts react with orthoesters at −78°C in the presence of boron trifluoride to give the three-component coupling product (Scheme 50, Table 6)[113]. Here again, incorporation of the organometallics and the electrophiles occurs regiospecifically at vicinal positions of the enone. Aminal esters may also be employed as electrophilic component. Other Lewis acids such as aluminum trichloride or titanium tetrachloride also accelerate the reaction, but are less effective than boron trifluoride (see Table 6).

Acetals are much less reactive than orthoesters. The condensation is made possible, however, when trimethylsilyl triflate is used in place of ordinary Lewis acid promoters (Scheme 50, Table 6)[133]. The enolates initially formed are probably converted into the silyl enol ethers, which are



Scheme 50. Three-component coupling of enone, organocopper reagent, and orthoester or acetal.

Table 6. Double vicinal CC-coupling of enones with organocopper reagents and orthoesters [a], aminal esters [a] or acetals [b].

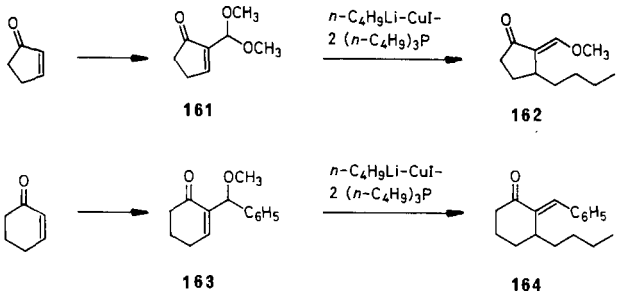
Enone	R_β	Third component	Yield [%]
2-Cyclohexenone	*n*-Butyl	Trimethyl orthoformate	63 [c, d]
2-Cyclohexenone	*tert*-Butyl	Trimethyl orthoformate	66 [d, e]
2-Cyclohexenone	Isopropenyl	Trimethyl orthoformate	60
2-Cyclopentenone	*n*-Butyl	Trimethyl orthoformate	86
2-Cyclopentenone	Isopropenyl	Trimethyl orthoformate	80
2-Cyclopentenone	*n*-Butyl	Triethyl orthoacetate [f]	60 [g]
4-(*tert*-Butyldimethylsiloxy)-2-cyclopentenone	*n*-Butyl	Trimethyl orthoformate	59
2-Cyclopentenone	(*Z*)-3-(*tert*-Butyldimethylsiloxy)-1-octenyl	Trimethyl orthoformate	69
2-Cyclopentenone	*n*-Butyl	Dimethylformamide dimethyl acetal [f]	58 [h]
2-Cyclopentenone	(*E*)-3-(*tert*-Butyldimethylsiloxy)-1-octenyl	Dimethylformamidedimethyl acetal	56
2-Cyclohexenone	*n*-Butyl	Benzaldehyde dimethyl acetal	76
2-Cyclohexenone	*n*-Butyl	Butyraldehyde dimethyl acetal	46
2-Cyclohexenone	*n*-Butyl	Acetone dimethyl acetal	73
2-Cyclohexenone	*tert*-Butyl	Benzaldehyde dimethyl acetal	61
2-Cyclohexenone	*tert*-Butyl	Butyraldehyde dimethyl acetal	42 [i]
2-Cyclohexenone	Methyl [j]	Benzaldehyde dimethyl acetal	75
5-Methyl-3-hexen-2-one	(*Z*)-4,4-Diethoxy-1-butenyl	— [k]	50
2-Cyclohexenone	(*Z*)-4,4-Diethoxy-1-butenyl	— [k]	43 [l]

[a] The Organocopper reagent was added at −78 °C. The enolate trapping was performed using stoichiometric amounts of an orthoester or aminal ester and boron trifluoride at −95 to −78 °C. [b] The Organocopper reagent was added at −78 °C. The enolate trapping was conducted using 1.5–3 equiv of an acetal and trimethylsilyl triflate at −78 °C to −40 °C. [c] *trans*-3-Butyl-2-(dimethoxymethyl)cyclohexanone. [d] The stereochemistry was determined by X-ray structure analysis of a crystalline derivative. [e] *trans*-3-*tert*-Butyl-2-(dimethoxymethyl)cyclohexanone. [f] Reaction at −40 °C to room temperature. [g] 3-Butyl-2-(1-ethoxyethylidene)cyclopentanone. [h] 3-Butyl-2-(dimethylaminomethylene)cyclopentanone. [i] Reaction at −78 to 0 °C. [j] CH_3MgBr (1 equiv) − Li_2CuCl_4 (0.1 equiv) was used for conjugate addition. [k] Intramolecular acetal trapping was performed at 15 °C. [l] Bicyclo[4.4.0]deca-1(10),7-dien-2-one was formed.

capable of undergoing the silyl triflate-catalyzed reaction[91,92] with acetals. The intramolecular variant of this reaction provides a novel annelation procedure.

4.5.3. Conjugate Addition of Organocopper Compounds to α-Alkoxyalkylated Enones

Application of the conjugate cuprate addition to α-(di)alkoxyalkylated α,β-unsaturated ketones allows preparation of authentic 3-alkyl-2-alkylidenealkanones. The utility of the new double vicinal CC-coupling process is demonstrated in Scheme 51[122]. The products, **162** and **164**, were obtained from **161** and **163** in 60 and 89% yield, respectively. This procedure is particularly useful for the synthesis of heterocyclic compounds[90].

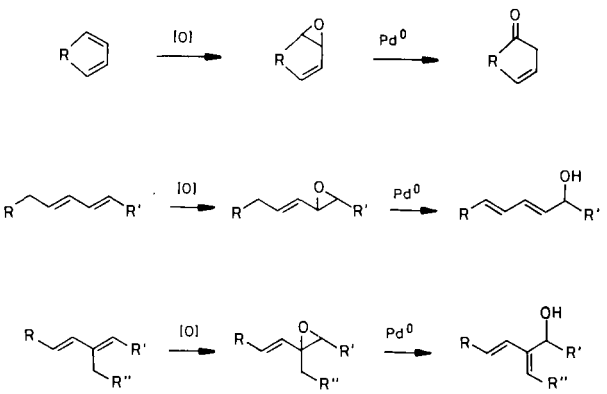


Scheme 51. Regiospecific synthesis of 2-alkylidene-3-alkylalkanones.

4.6. Palladium(0)-Catalyzed Isomerization of Epoxides

4.6.1. Isomerization of the 1,2-Epoxides of 1,3-Dienes

In connection with our search for access to the prostaglandin intermediates starting from cyclopentadiene, we have also examined the isomerization of the 1,2-epoxides of 1,3-dienes. This reaction is catalyzed by tetrakis(triphenylphosphane)palladium(0)[48a]. The course of the reaction appears to be highly dependent on the structures and substitution patterns of the substrates (Scheme 52). Epoxides



Scheme 52. Palladium(0)-catalyzed isomerization of the 1,2-epoxides of 1,3-dienes.

derived from 1,3-dienes afford the corresponding 3-cycloalkenones. Noteworthy, is the selective formation of β,γ-unsaturated ketones, which are usually less stable than their α,β-unsaturated analogues. The epoxy compounds derived from flexible 1,3-dienes isomerize, with shifting of the double bond, to give the dienols; the overall transformation can be formally regarded as an ene-reaction or vinylogous ene-reaction of 1,3-dienes caused by a singlet oxygen atom[134]. Examples of the catalyzed reaction are given in Table 7. The divergence of the reaction pathway results from differences in the structures of the organopalladium intermediates. Zwitterions of the type **165**, which are formed by nucleophilic attack of the palladium(0) reagent on the epoxides of the cyclic dienes, readily undergo hydrogen reorganization via palladium hydride species[135],

Table 7. Palladium(0)-catalyzed reaction of the 1,2-epoxides of 1,3-dienes [a].

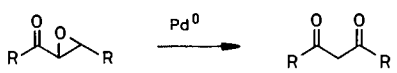
Epoxide	T [°C] (t [h])	Product	Yield [%]
3,4-Epoxycyclopentene	0–10 [b, c] (2)	3-Cyclopentenone	88
3,4-Epoxycyclohexene	25 [c] (3)	3-Cyclohexenone	94
3,4-Epoxycycloheptene	120–140 [d]	3-Cycloheptenone	56
3,4-Epoxycyclooctene	120 [e] (22)	3-Cyclooctenone	74
3,4-Epoxycyclododecene [f]	120 [g] (24)	3-Cyclododecenone	79 [f]
		2,4-Cyclododecadien-1-ol	13 [f]
(*E*)-*trans*-7,8-Epoxy-5-dodecene	110 [e] (24)	6,8-Dodecadien-5-ol	95 [f]
4,5-Epoxy-2,5-dimethyl-2-hexene	130 [g] (36)	(*E*)-2,5-Dimethyl-3,5-hexadien-2-ol	81
3,4-Epoxy-2,3-dimethyl-1-butene	60 [h] (24)	3-Methyl-2-methylene-3-buten-1-ol	70
3,4-Epoxy-3,7-dimethyl-9-methoxy-1-nonene	60 [e] (24)	9-Methoxy-3-methylene-7-methyl-1-nonen-4-ol	81
3,4-Epoxy-2,3-tetramethylene-1-butene	50 [e] (24)	(6-Methylene-1-cyclohexenyl)methanol	90
1-Vinyl-1,2-epoxycyclohexane	60 [e] (25)	2-Vinyl-2-cyclohexen-1-ol	39

[a] Reaction was carried out under argon atmosphere using 0.1–1 mol-% of tetrakis(triphenylphosphane)palladium(0) as catalyst. In most cases, some triphenylphosphane (1–2 equiv referred to the catalyst) was added. [b] With only 0.00013 mol-% of palladium(0)catalyst. No triphenylphosphane was added. [c] Dichloromethane as solvent. [d] Vapor-phase reaction. [e] In THF. [f] Stereoisomers. [g] In benzene. [h] In ether.

giving β,γ-unsaturated ketones, whereas the alkoxypalladium(II) complexes of type **166**, formed from the structurally flexible substrates, cause hydrogen transfer from RCH_2 to Pd and, hence, formation of the dienol. This reaction provides a new means for regiospecific oxygenation of 1,3-dienes. That the intermediate **166** could be trapped by some stabilized carbanions[136], extends the usefulness of this catalytic reaction.

4.6.2. *Synthesis of β-Diketones from Epoxy Ketones*

The efficiency of the epoxide isomerization occurring under aprotic, neutral conditions is due to the excellent nucleophilicity of palladium(0) species and the ability of palladium(II) species to carry hydrogen. These properties have been exploited for the synthesis of β-diketones (Scheme 53, Table 8)[139]. Thus, on heating a toluene solution of a 2,3-epoxy ketone and catalytic amounts of tetrakis(triphenylphosphane)palladium(0) and 1,2-bis(diphenylphosphino)ethane at 80 to 140°C, the β-diketone was formed. Table 8 shows some examples, including a high-yield synthesis of 1,3-cyclopentanedione, a prized compound[138].



Scheme 53. Palladium(0)-catalyzed isomerization of epoxy ketones to β-diketones.

Table 8. Palladium(0)-catalyzed isomerization of α,β-epoxy ketones to β-diketones [a].

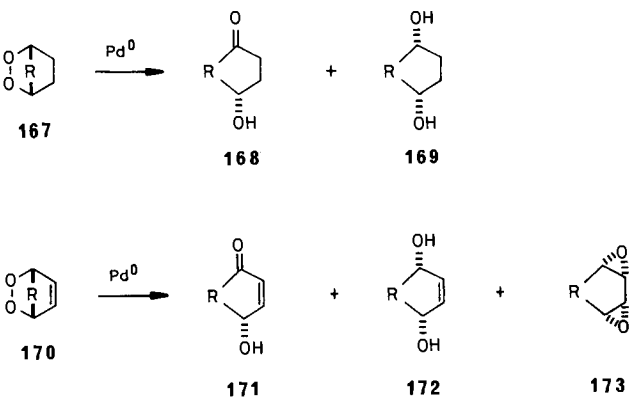
Epoxy ketone	Product	Yield [%]
trans-3,4-Epoxy-2-pentanone	2,4-Pentanedione	81
trans-3,4-Epoxy-5-methyl-2-hexanone	5-Methyl-2,4-hexanedione	80
trans-4,5-Epoxy-6-tridecanone	4,6-Tridecanedione	90
trans-1,2-Epoxy-1-phenyl-3-nonanone	1-Phenyl-1,3-nonanedione	82
trans-2,3-Epoxy-1,3-diphenyl-1-propanone	1,3-Diphenyl-1,3-propanedione	84
trans-2,3-Epoxycyclododecanone	1,3-Cyclododecanedione	54
2,3-Epoxycyclooctanone	1,3-Cyclooctanedione	52
2,3-Epoxycycloheptanone	1,3-Cycloheptanedione	60
2,3-Epoxycyclohexanone	1,3-Cyclohexanedione	62
5-Isopropyl-2-methyl-2,3-epoxycyclohexanone	5-Isopropyl-2-methyl-1,3-cyclohexanedione	18
2,3-Epoxycyclopentanone	1,3-Cyclopentanedione	94

[a] Reaction was carried out using tetrakis(triphenylphosphane)palladium(0) and 1,2-Bis(diphenylphosphino)ethane (1.5–10 mol-%) in toluene at 80–140°C under argon.

4.7. Transition Metal-Catalyzed Reactions of 1,4-Epidioxides

4.7.1. *Palladium(0)-Catalyzed Reactions*

1,4-Epidioxides (endoperoxides) have become increasingly important as synthetic intermediates[139]. Dye-sensitized photooxygenation of 1,3-dienes affords 2,3-unsaturated 1,4-epidioxides in good yields[134], from which the saturated analogues are obtainable by diimide reduction[140]. First, we chose to concentrate on the catalytic reaction with a soluble palladium(0) complex, which has a tendency to recycle the metal by way of a two-electron redox process[48a, 137]. Actually, when purified epidioxides of the type **167** [R = $(CH_2)_{1-4}$] were treated with a catalytic amount of tetrakis(triphenylphosphane)palladium(0) in dichloromethane or benzene, the 4-hydroxy ketone **168** and the 1,4-diol **169** were formed as the major products via competing two- and one-electron exchange reactions (Scheme 54, Table 9)[48b, 141]. 2,3-Dehydro-1,4-epidioxides **170** behave similarly[48b] and give **171** and **172**. In some cases, the diepoxide **173** is also formed. The reactivity and selectivity are highly influenced by the ring systems.



Scheme 54. Palladium(0)-catalyzed reaction of 1,4-epidioxides.

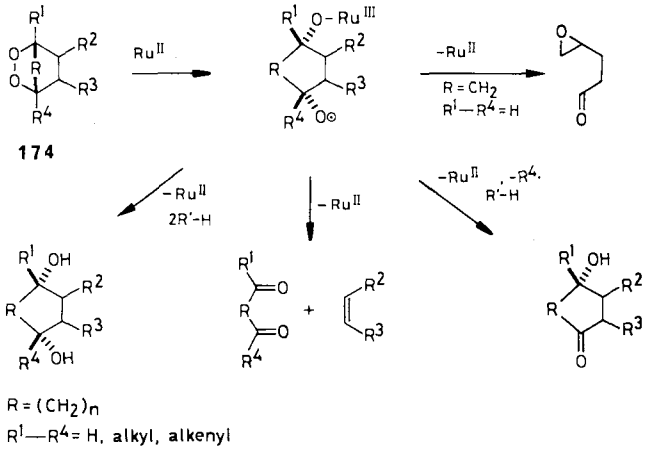
Table 9. Palladium(0)-catalyzed reaction of1,4-epidioxides [a].

Epidioxide	T [°C]	t [h]	Products	Yield [%]
1,3-Epidioxycyclopentane	28	2.5	3-Hydroxycyclopentanone	40
			Levulinaldehyde	
			Levulinaldehyde	25
			1,3-Cyclopentanediol	20
1,4-Epidioxycyclohexane	60	5	4-Hydroxycyclohexanone	44
			1,4-Cyclohexanedione	4
			1,4-Cyclohexanediol	39
1,4-Epidioxycycloheptane	60	10	4-Hydroxycycloheptanone	62
			1,4-Cycloheptanedione	13
			1,4-Cycloheptanediol	25
1,4-Epidioxycyclooctane	65 [b]	15	4-Hydroxycyclooctanone	73 [c]
			1,4-Cyclooctanediol	23
3,5-Epidioxycyclopentene	4 [d]	20	4-Hydroxy-2-cyclopentenone	54
			4-Cyclopentene-1,3-diol	4
3,6-Epidioxycyclohexene	50–60	5	4-Hydroxy-2-cyclohexenone	39
			2-Cyclohexene-1,4-diol	30
			syn-1,2:3,4-Diepoxycyclohexane	8
3,5,5-Trimethyl-3,6-epidioxycyclohexene	60	46	4-Hydroxy-4,6,6-trimethyl-2-cyclohexenone	68
			1,5,5-Trimethyl-2-cyclohexene-1,4-diol	6
			syn-1,2:3,4-Diepoxy-4,6,6-trimethylcyclohexane	24
3,8-Epidioxycyclooctene	60 [b]	29	4-Hydroxy-2-cyclooctenone	51 [c]
1,4-Epidioxy-4-methyl-1-phenyl-2-pentene	100	15	(*E*)-4-Hydroxy-4-methyl-1-phenyl-2-penten-1-one	66

[a] Reaction was carried out with 5–10 mol-% of tetrakis(triphenylphosphane)palladium(0) in dichloromethane. [b] Benzene as solvent. [c] As hemiacetal. [d] The catalyst and the substrate were mixed at −78°C.

4.7.2. *Ruthenium(II)-Catalyzed Reactions*

Dichlorotris(triphenylphosphane)ruthenium(II), which is soluble in aprotic organic solvents, is another interesting catalyst. This complex is capable of inducing reactions via one-electron exchange mechanisms[142]. As outlined in Scheme 55, when the substrates of type **174** are exposed to a catalytic amount of the ruthenium catalyst, the O–O linkage is cleaved and a mixture of products arising from fragmentation, reduction, and disproportionation is obtained[143]. The reactions proceed via radical intermediates, but they behave differently than photolytically or thermolytically free radicals. The reaction profile is interpretable in terms of "inner-sphere radicals"[142].



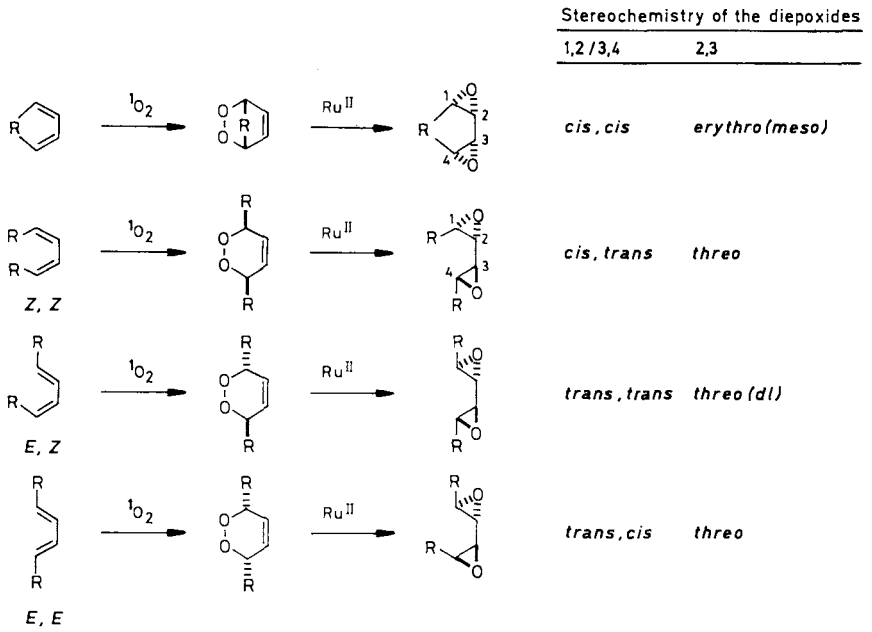
Scheme 55. Ruthenium(II)-catalyzed reaction of saturated 1,4-epidioxides.

Table 10. Ruthenium(II)-catalyzed reaction of 2,3-dehydro-1,4-epidioxides [a].

Substrate	Products	Yield [%]
3,5-Epidioxycyclopentene [b]	*syn*-1,2:3,4-Diepoxycyclopentane	78
3,6-Epidioxycyclohexene	*syn*-1,2:3,4-Diepoxycyclohexane	91
3,6-Epidioxy-3,5,5-trimethylcyclohexene	2,3-*erythro*-1,2:3,4-Diepoxy-1,5,5-trimethylcyclohexane	97
3,7-Epidioxycycloheptene	*syn*-1,2:3,4-Diepoxycycloheptane	98
3,4-Dioxabicyclo[4.4.0]dec-1(6)-ene [c]	2,3-*threo*-2,3-Tetramethylene-1,2:3,4-diepoxybutane	1
[4.4.0]dec-1(6)-ene [c]	4,5,6,7-Tetrahydroisobenzofuran	76
cis-3,6-Dimethyl-1,2-dioxa-4-cyclohexene	3,4-*threo*-2,3-*trans*:4,5-*cis*-Diepoxyhexane	21
	2,5-Dimethylfuran	43
cis-3,6-Dibutyl-1,2-dioxa-4-cyclohexene	6,7-*threo*-5,6-*trans*:7,8-*cis*-Diepoxydodecane	48
	6,7-*erythro*-5,6-*trans*:7,8-*trans*-Diepoxydodecane	5
	2,5-Dibutylfuran	38
trans-3,6-Dibutyl-1,2-dioxa-4-cyclohexene	6,7-*threo*-5,6-*trans*:7,8-*trans*-Diepoxydodecane	30
	6,7-*erythro*-5,6-*trans*:7,8-*cis*-Diepoxydodecane	6
	2,5-Dibutylfuran	40
cis-3,6-Diphenyl-1,2-dioxa-4-cyclohexene	2,3-*threo*-1,2-*trans*:3,4-*cis*-Diepoxy-1,4-diphenylbutane	44
	2,5-Diphenylfuran	34
cis-3,6-Di-*tert*-butyl-1,2-dioxa-2-cyclohexene	4,5-*threo*-3,4-*trans*:5,6-*cis*-Diepoxy-2,2,7,7-tetramethyloctane	50
	6-Hydroxy-2,2,7,7-tetramethyl-4-octen-3-one	23 [d]

[a] Reaction was conducted with 1–8 mol-% dichlorotris(triphenylphosphane)ruthenium(II) in dichloromethane at 0–45°C under argon atmosphere. [b] Reaction at −25°C. [c] Reaction at −78°C. [d] A 1:1 mixture of the *Z*- and *E*-isomers.

In the case of 2,3-unsaturated 1,4-epidioxides, on the other hand, highly selective changes take place in the molecular framework. The bicyclic substrates are cleanly converted into the 2,3-*erythro*-1,2;3,4-diepoxides[143]. The monocyclic substrates generally give mixtures of the diepoxide and furan derivatives (Table 10)[144]. As illustrated in Scheme 56, the conversion of epidioxide into diepoxide takes a characteristic stereochemical course. Thus, epidioxides derived from (*E,E*)- or (*Z,Z*)-1,3-dienes produce predominantly the 1,2-*cis*-3,4-*trans*-diepoxides, whereas the epidioxides of (*Z,E*)-dienes afford the *trans,trans*-diepoxides. All these products—in contrast to the bicyclic system—have 2,3-*threo* relative configurations. This strikingly contrasting stereochemistry originates from differences in the ground-state geometry of the substrates: C_s-symmetry of the bicyclic endoperoxides and the C_2 chirality of the monocyclic dioxy compounds.

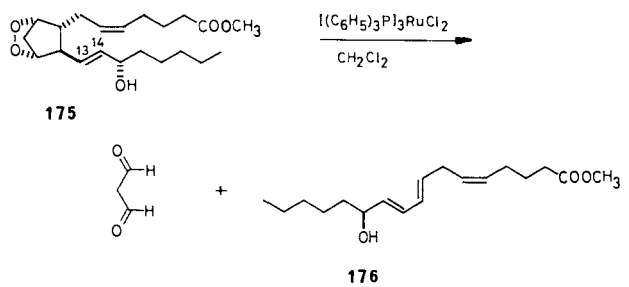


Scheme 56. Ruthenium(II)-catalyzed formation of 1,2 : 3,4-diepoxides.

4.7.3. Transition Metal-Catalyzed Transformations of Prostaglandin Endoperoxides

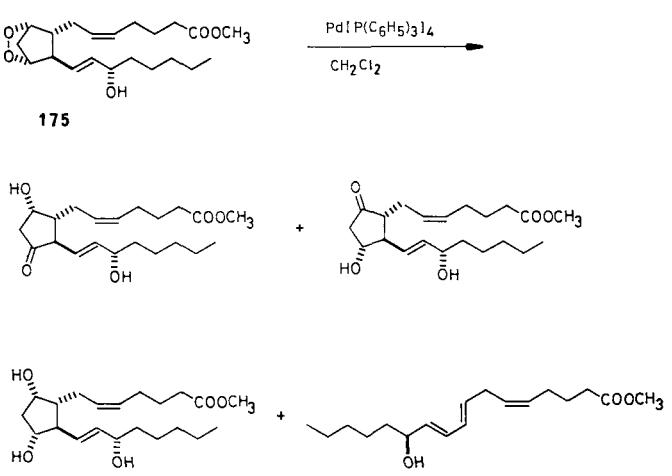
Prostaglandin endoperoxides serve as key substances in prostaglandin biosynthesis[1], and a variety of hypotheses have been advanced for their enzymatic transformation into primary prostaglandins, prostacyclin, and thromboxanes[145]. We have been intrigued by the homogeneous catalysis with transition metals possessing known chemical properties, since such an approach could provide some chemical interpretation of the mechanism of bioconversion[146].

The reaction of PGH_2 methyl ester **175** with 3 mol-% of dichlorotris(triphenylphosphane)ruthenium(II) catalyst in dichloromethane is remarkably clean, and only malonaldehyde and methyl (5*Z*,8*E*,10*E*,12*S*)-12-hydroxy-5,8,10-heptadecatrienoate (**176**, HHT methyl ester) are formed (Scheme 57)[143]. The fragmentation is stereospecific in nature with respect to the side-chains on C-8 and C-12. Obviously, the presence of the double bond between C-13 and C-14 facilitates the oxygen radical-induced fragmentation (cf. Scheme 55). No primary prostaglandin methyl esters are formed by this reaction. It should be added that thromboxane synthetase converts PGH_2 into a mixture of thromboxane A_2 and HHT[147].



Scheme 57. Stereospecific fragmentation of PGH_2 methyl ester **175** catalyzed by a ruthenium(II) catalyst.

As shown in Scheme 58, catalytic decomposition of PGH_2 methyl ester **175** with 10 mol-% of tetrakis(triphenylphosphane)palladium(0) in dichloromethane gives rise to a mixture of methyl esters of PGD_2 (17%), PGE_2 (11%), $PGF_{2\alpha}$ (41%), and HHT (4%). Here primary prostaglandins are the major products[148].



Scheme 58. Palladium(0)-catalyzed reaction of PGH_2 methyl ester **175**.

5. Outlook

Contributions to prostaglandin research can come from various scientific disciplines independently or cooperatively. One of the major challenges facing the synthetic organic chemist is to find an efficient entry to these substances which satisfies the demands of industrial applicability. We have developed a new purposive entry to prostaglandins. Here, adequate methodologies were available from the field of organometallic chemistry to perform the

vital functions in its convergency and to overcome all the major obstacles which existed at the threshold of prostaglandin synthesis. The present method is direct, efficiently stereocontrolled, general, and flexible. It is capable, not only of producing natural prostaglandins expenditiously but also of creating a variety of artificial analogues by the same technique.

The prostaglandin family controls a wide variety of physiological responses in body tissues, especially relating to regulation of functions of the circulatory system, respiratory and digestive organs etc. With the progress being made in our understanding of their pharmacological importance, several natural prostaglandins and their analogues are already available on the market for therapeutic use. For instance, PGE_2 and $PGF_{2\alpha}$ are drugs for inducing labor in women at term, for first-trimester abortion, for paralytic ileus, etc. PGE_1, a powerful vasodilator, is used for the treatment of severe peripheral vascular diseases such as Bürger disease and Raynaud's disease. PGI_2 is used for kidney dialysis and prevention of platelet loss in cardiopulmonary operations. In addition, numerous other clinical trials have been made and the outlook is bright. Further, $PGF_{2\alpha}$ and its analogues are now used for the treatment of reproductive difficulties in livestocks and for the synchronization of ovulation in breeding management. Obviously animal husbandry demands a plentiful supply of such synthetic materials. The efficiency of the syntheses via Corey lactones has been amply demonstrated by supplying sufficient material to meet current demands.

The spectrum of biological activities of the prostaglandins is unique and broad. PGI_2 and TXA_2 exhibit extremely potent but opposite behavior. These compounds are labile under physiological conditions; their half-lives are about five minutes and 30 seconds, respectively. The design and synthesis of stable PGI_2 analogues are subjects of current interest. Since intestinal motility and diarrhea occur as side effects, a separation of the activies and the specific effects are highly desirable through chemical modification of the molecules.

Prostaglandins and related compounds from the arachidonic acid cascade continue to attract a great deal of attention from biochemists and biomedical scientists. Some prostaglandins are now recognized to have a profound relation to cancer[104, 149] and brain physiology[150]. The prostaglandins have also received entomological interest since the discovery of PGE_2 in female crickets[151]. Recent information about prostaglandins in gonadal histology has now been extended from a variety of vertebrates to the maturation or spawning of marine invertebrates[152].

We hope that the chemical process presented here is viable as the second practical synthesis, and that it will beneficially contribute to the progress being made in this wide field through the efficient supply of known or newly created biologically significant substances.

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Asymmetric Diels-Alder and Ene Reactions in Organic Synthesis

New Synthetic Methods (48)

By Wolfgang Oppolzer*

Rapidly accumulating evidence shows the value of asymmetric Diels-Alder and ene reactions for the syntheses of enantiomerically pure molecules. This article presents a systematic and critical treatment of various stereoface-differentiating principles, including very recent spectacular advances. The chiral information is mainly provided by covalently bound auxiliaries, some of which are crystalline, inexpensive, and readily available from naturally occurring monoterpenes, hydroxy acids, amino acids, steroids, and sugars. Nondestructive transfer of chirality leads to the efficient creation of up to four chiral centers with predictable relative and absolute configurations. Regenerative cleavage of the auxiliary group from the diastereomerically pure adducts furnishes a range of polyfunctional, optically pure building blocks. Their synthetic potential is illustrated by strategic applications to the syntheses of physiologically interesting, chiral natural products such as prostaglandins, antibiotics, terpenoids, shikimic acid, alkaloids, and kainoids.

1. Introduction

The efficient construction of enantiomerically pure, structurally complex molecules is a fundamental challenge in organic synthesis. Only recently have extensive efforts been made to induce asymmetry in carbon-carbon bond forming reactions[1]. Among these the Diels-Alder reaction merits particular attention. Accordingly, this review focuses on the achievement of absolute configurational control in Diels-Alder reactions, underscoring various principles and illustrating their strategic applications to natural product syntheses. Furthermore, the employment of analogous concepts in asymmetric ene reactions is outlined. Pertinent examples are selected based on the criteria of high stereodifferentiation and removability of the chiral control group from the product. Mechanistic discussions provide insight into the three-dimensional nature of the corresponding transition states, assuming the operation of kinetic control.

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2. Asymmetric Diels-Alder Reactions—General

Since its discovery in 1928 the Diels-Alder reaction has been refined to become one of the most powerful tools in organic synthesis[2]. A most attractive feature is the simultaneous, regioselective formation of two bonds leading to the creation of up to four chiral centers at the binding sites with largely predictable relative stereochemistry. Studies of the control of the absolute topicity started in 1961, but substantial progress has only been achieved in recent years. At present, this field is expanding rapidly, which justifies a selective rather than exhaustive review.

To illustrate the overall stereochemical features, we mention the first reported example of a strategic application in synthesis.

Addition of 5-(methoxymethyl)cyclopentadiene **1a** to acrylic acid **2a** proceeded *endo*-selectively and *anti* with respect to the diene substituent[3]. Consequently, the relative configuration of the four new chiral centers in **3a** is determined and, of four possible diastereoisomers, one is formed selectively. As expected, the diene added at the same rate to the two enantiotopic dienophile π-faces affording a 1:1-mixture of the enantiomers (1*R*)-**3a** and

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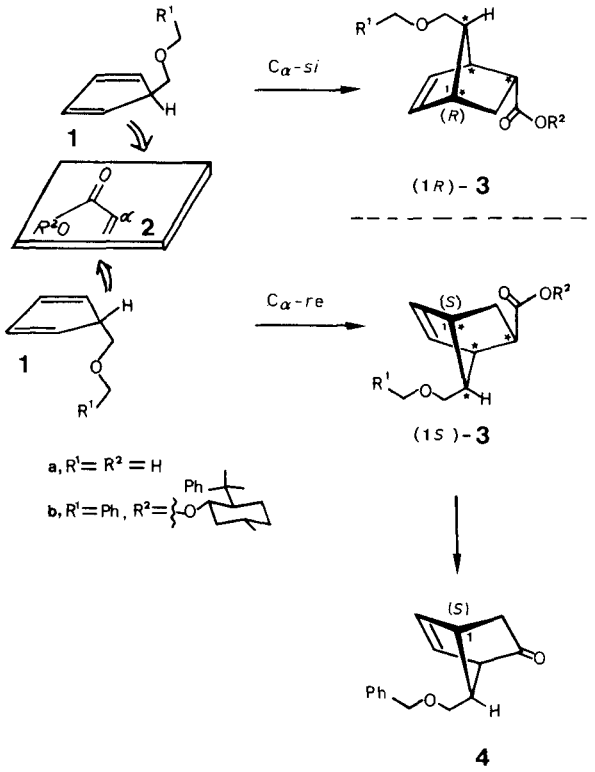


(1*S*)-**3a**. Since only the (1*S*)-enantiomer is suitable for the synthesis of prostaglandins, exclusive diene addition from the C_α-*re*-face was required. Indeed, attachment of an appropriate chiral ester group R^2 to the dienophile **2** caused steric shielding of the now diastereotopic C_α-*si*-face thereby directing the $AlCl_3$-promoted diene addition to the C_α-*re*-face. As a result of this π-face differentiation, the desired (1*S*)-**3b** was obtained from **2b** in significant excess over the undesired (1*R*)-isomer. Degradation of this mixture involving cleavage of the chiral control element R^2 furnished ketone **4** in high enantiomeric purity[4]. This example also serves to illustrate the definition of diastereomeric excess (d.e.) used throughout this review. For instance, a hypothetical ratio (1*S*)-**3b**/(1*R*)-**3b** = 95 : 5 amounts to 90% diastereomeric excess (d.e.) of (1*S*)-**3b** over (1*R*)-**3b** and leads to the (1*S*)-ketone **4** in 90% enantiomeric excess (e.e.). Accordingly, the π-face differentiation-related diastereomeric excess (e.g. 90% d.e. of (*S*)-**3b**) translates in general into enantiomeric excess (e.g. 90% e.e. of **4**) after removal of the chiral auxiliary.

The above example demonstrates the addition of a prochiral diene to a chiral dienophile which carries a removable chiral auxiliary. Further options for π-topological differentiation in Diels-Alder reactions include the temporary attachment of a chiral control group to the diene or, more elegantly, the employment of a chiral catalyst. So far the stoichiometric use of covalently bound chiral control groups has proved to be more efficient and predictable. In practical terms, the ideal prosthetic group should meet the following criteria:

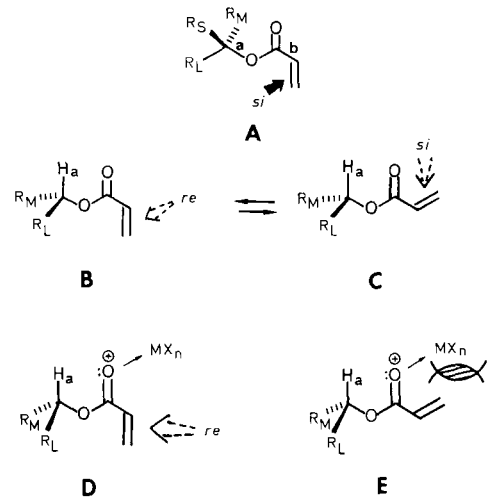
1) Provide a wide range of Diels-Alder adducts in high chemical yield with virtually quantitative and predictable π-face stereodifferentiation.
2) Both enantiomers or alternative topological counterparts should be readily available.
3) Be capable of efficient attachment and nondestructive removal from the adduct with complete retention of the induced configuration.
4) Permit facile purification of the major cycloadduct to almost 100% d.e.
5) Impose crystallinity on intermediates and products.

Consequently, success in this research area relies on logical design and imagination, but also on numerous empirical parameters.

3. Chiral Dienophiles

3.1. Acrylates

The vast majority of work on asymmetric Diels-Alder reactions deals with additions of 1,3-dienes to chiral, conjugated carboxylic esters. In this context, the relevant conformers of acrylates derived from secondary alcohols are discussed briefly.

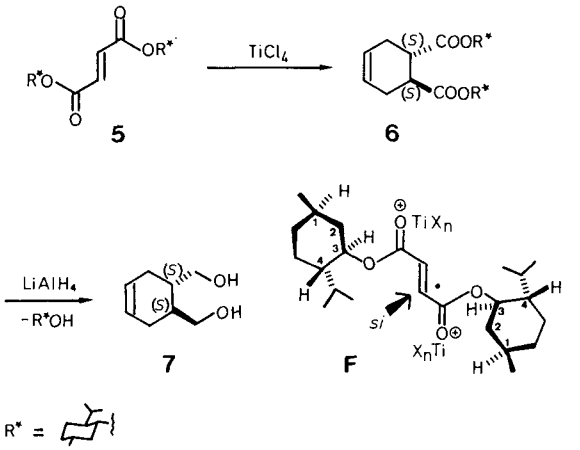


Conformation **A**, postulated by *Prelog* et al.[5], implies an *anti*-orientation of the large substituent R_L and the C=O group which is antiplanar to the olefinic bond. This model differs slightly from conformer **B**, which, according to X-ray data[6], exhibits a synperiplanar C–H_a/C=O-relationship in the crystal. In solution, however, spectroscopic evidence[7] indicates an equilibrium between conformers **B** and **C**, where the synplanar C=O/C=C-disposition of the latter is disfavored by only $\Delta H = 0.32$ kcal/mol. If the diene adds exclusively to the π-face opposite the larger substituent, conformers **B** and **C** display reversed topicity. Consistent with this element of unpredictability, no thermal Diels-Alder reactions of acrylates have ever surpassed the threshold of 65% d.e. However, the situation changes dramatically when the acrylate coordinates to a Lewis acid. Supported by the results of X-ray[8] and spectroscopic studies[9], we assume predominant coordination of various Lewis acids (notably $TiCl_4$ and $SnCl_4$) with the carbonyl oxygen *anti* to the ester oxygen. This precludes conforma-

tion **E** on steric grounds and secures the C=O/C=C *anti*-conformation **D**. Moreover, Lewis-acid coordination to acrylates increases the regio- and *endo*-selectivity as well as the rate of their [4+2]-addition to 1,3-dienes. As a result of this advantageous coincidence of effects, successful asymmetric Diels-Alder reactions are generally carried out at low temperatures in the presence of a Lewis acid. This dichotomous influence of coordination on the activation energies for conformer interconversion and cycloaddition is also of predictive value for the rational design of chiral control groups. One limitation, nevertheless, should be mentioned. If the diene adds to the complex **D** from the side opposite to the large group R_L, tetragonalization of the enoate centers may be sterically hindered. In fact, enoates which carry a bulky ester substituent generally show a decreased dienophile reactivity which restricts their application to asymmetric Diels-Alder additions of mutually reactive diene and dienophile partners.

3.1.1. Addition of Bis(menthyl) Fumarate to 1,3-Butadiene

In 1963 *Walborsky* published his pioneering work on the addition of bis(menthyl) fumarate **5** to 1,3-butadiene promoted by Lewis acids, affording the cyclohexene derivative **6**[10]. Optimal results (80% yield, 78% d.e.) were obtained using $TiCl_4$ (1 mol per mol **5**) in toluene at +25°C. The reported rationalization refers to the Prelog model **A** involving conformation **F**. Regardless of the validity of this model, it should be considered that the high level of diastereodifferentiation relies on the cooperative influence of *two* chiral prosthetic groups (R* = (−)-menthyl).



3.1.2. Additions of Acrylates Derived from (−)-Menthol to Cyclopentadiene

Employment of only *one* menthyl auxiliary, as in the addition of menthyl acrylate to (the even more reactive) cyclopentadiene at lower temperatures (**8**→**9**, R=H), does not show the same degree of stereoselection as indicated in Table 1 (entry 3[11]). Early studies (entries 1, 2)[12,13] relied entirely on chiroptic comparisons, which are insufficient to assess the extent of an induction[1a]. The significantly higher diastereotopic face differentiation exerted by the 8-phenylmenthyl auxiliary was first reported to result in an

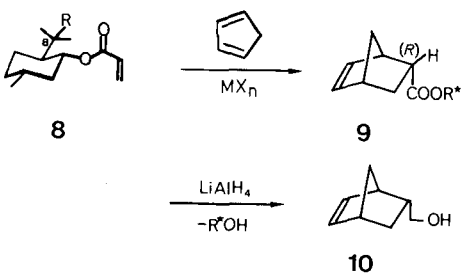
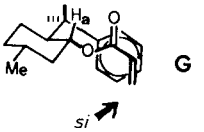


Table 1. Examples of reaction **8**→**9** in the presence of MX_n at −20°C in CH_2Cl_2.

Entry	R	**8** : MX_n	MX_n	Yield [%]	*endo* [%]	d.e. [%]
1 [a]	H	1 : 1.0	$SnCl_4$	76	89	41
2 [b]	H	1 : 0.43	$BF_3 \cdot OEt_2$	74–81	95	74
3	H	1 : 1.5	$TiCl_4$	65	92	62
4	Ph	1 : 1.5	$SnCl_4$	[c]	[c]	(99)
5	Ph	1 : 1.5	$SnCl_4$	95	84	89
6	Ph	1 : 1.5	$TiCl_4$	83	89	90
7	Ph	1 : 0.7	$AlCl_3$	89	91	65

[a] At 4–8°C in toluene. [b] At 0°C. [c] Not reported [4].

induction of 99% d.e. based on the optical rotation of **10**[4]. This value was subsequently corrected to 89% (entries 4, 5)[11] as a result of a study which also showed how significantly the extent of *si*-face selection depends (entries 5–7) on the nature of the Lewis acid. The topological bias of the 8-phenylmenthyl group reported by *Corey* et al.[4] represents without doubt a landmark in asymmetric synthesis. It



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is readily rationalized by postulating a conformationally rigid cyclohexane **G** featuring an acrylate conformation **D** and *re*-face shielding by the *α-trans* 1-methyl-1-phenylethyl group[14]. The enhanced diastereoselection may be a consequence of complementary steric and aryl-acrylate π-stacking effects. Nevertheless, limitations include the oily nature of (−)-8-phenylmenthol, the need for careful purification by medium pressure chromatography during its preparation from (+)-pulegone, and the difficult accessibility of its *re*-face directing (+)-enantiomer[15].

3.1.3. Addition of (S)-(+)-1,2,2-Trimethylpropyl Acrylate to Cyclopentadiene

A comparatively efficient C_α-*re*-face directing auxiliary had been reported previously. Thus, $BF_3 \cdot OEt_2$-induced addition of the ester **12** to cyclopentadiene furnished the (5*S*)-adduct **13** with high *endo*- and π-face stereoselectivity[13]. The initially reported modest yield (Table 2, entry 1) has been improved to 75% more recently (Table 2, entry 2)[16]. It is worth noting that the absolute topicity is consistent with diene attack at the side opposite to the bulky *tert*-

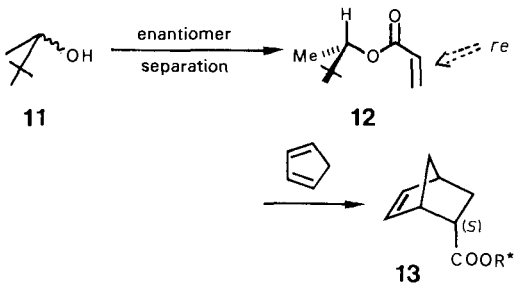


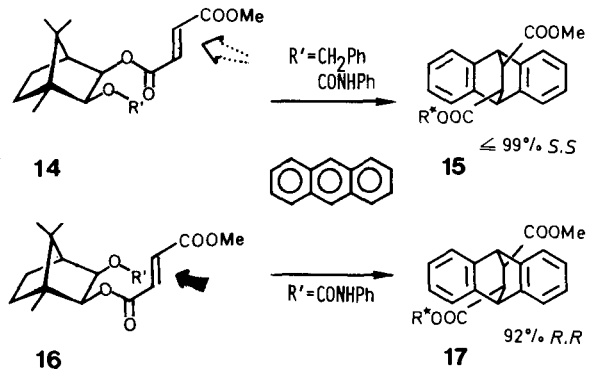
Table 2. Examples of the reaction **12** → **13** in the presence of $BF_3 \cdot OEt_2$ (1 mol per mol **12**) at −70°C in CH_2Cl_2.

Entry	Yield [%]	*endo* [%]	d.e. [%]	Ref.
1	44	>95	88	[13]
2	75	97	80–85	[16]

butyl group of acrylate conformers **B** or **D** but *not* **A**. The practical applicability suffers from the necessary separation of the oily auxiliary alcohol **11** from its enantiomer.

3.1.4. Additions of Fumarates Derived from 3-Hydroxyisoborneol to Anthracene

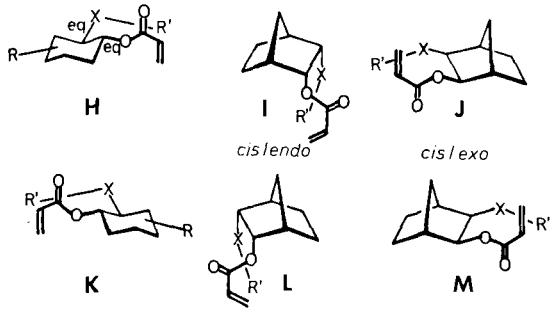
In the course of a model experiment, fumarates **14** and **16** were added efficiently to anthracene at −30°C in CH_2Cl_2 in the presence of $AlCl_3$ (1 mol per mol educt)[17].



The shielding of the fumarate π-faces by the benzyloxy- or *N*-phenylcarbamoyl substituents led to the (11*S*,12*S*)-adduct **15** (from **14**) in up to 99% d.e. or to the (11*R*,12*R*)-isomer **17** (from **16**) in up to 92% d.e.

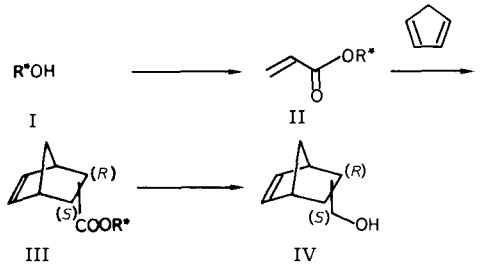
3.2. Working Concept for the Development of π-Face Differentiating Acrylates

The properties of phenylmenthol stimulated a search for more practical auxiliary alcohols: cyclohexanols locked in a chair conformation (cf. **H** and **K**) and conformationally rigid cyclopentanols[14a]. Accordingly, a number of studies focused on the *si*-face directing acrylates **H**, **I**, and **J** and their *re*-face directing counterparts **K**, **L**, and **M**.

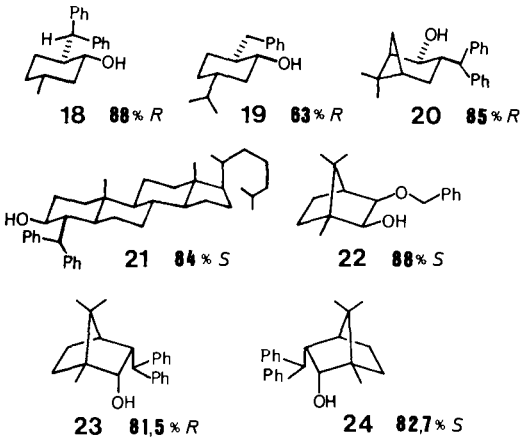


3.2.1. Acrylates of the Types H to M

Using the guidelines in Section 2, a number of alcohols **I** were prepared and converted into the acrylates **II**. To compare the sign and extent of the topological bias provided by each auxiliary, the Lewis-acid promoted addition to cyclopentadiene (**II** → **III**) served as a test reaction.

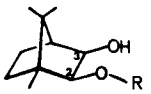


Acrylates from Various Auxiliary Alcohols: Alcohols **18** to **24** represent a cross-section of various, chiral auxiliary compounds which emerged initially from this work. $TiCl_4$-mediated additions of their acrylates **II** to cyclopentadiene afforded, predictably, either the (5*R*)- or the (5*S*)-2-norbornene adducts **III** with up to 88% diastereoselection[14].



Acrylates from cis-3-Hydroxyisobornyl Ethers: Pursuing the hypothetical role assigned to aryl/acrylate π-stacking and exploiting the ready availability of (+)- and (−)-camphor, the acrylates of the diphenylmethyl, α-naphthylmethyl, and β-naphthylmethyl ethers **25a**–**c** were added to cyclopentadiene. Whereas attempted catalysis by $TiCl_4$ failed because of rapid ether cleavage, high chemical

yields and up to 92% d.e. (Table 3) were conveniently obtained using the mild Lewis acid $TiCl_2(OiPr)_2$ [$TiCl_4$/$Ti(OiPr)_4$, 1 : 1].



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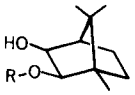

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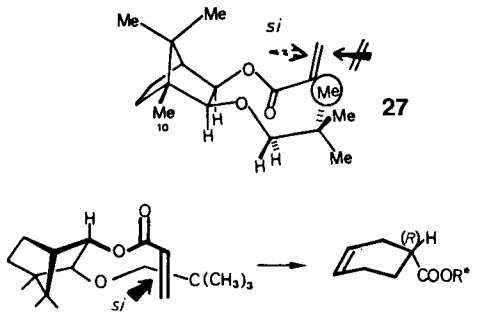
Table 3. Examples of the reaction of acrylates **II** derived from alcohols **I** (*cis*-3-hydroxyisonorbornyl ethers **25** and **26**) with cyclopentadiene to give adducts **III** (for conditions, see text).

Entry	I	R	Yield [%]	Adduct III *endo* [%]	C-5	d.e. [%]
1	**25a**	CH_2Ph	74	95	*R*	91
2	**25b**	2-Naphthylmethyl	98	95	*R*	92
3	**25c**	1-Naphthylmethyl	97	93	*R*	88
4	**25d**	Neopentyl	94	96	*R*	99.3
5	**26**	Neopentyl	98	95	*S*	99.3

On testing the effect of steric bulk on acrylate π-face shielding, it was found that the neopentyl ether **25d** displayed a dramatically superior chirality directing ability[18] which is considerably greater than that of 8-phenylmenthol. Inspection of models having a staggered conformation of the neopentyl ether chain (consistent with X-ray-data[19]) indeed revealed that the *tert*-butyl group sterically blocks the C_α-*re*-face in the acrylate **27**.



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From the practical standpoint, it is worthwhile mentioning that the low melting, but crystalline auxiliaries **25d** and **26** are readily accessible from either (+)- or (−)-camphor in 60% overall yields. Their acrylates provide either the (5*R*)- or the (5*S*)-adducts **III** in 94 to 98% chemical yield with 93 to 96% *endo*-selectivity and with over 99% diastereofacial differentiation (Table 3). Moreover, the auxiliaries are nondestructively removed from the cycloadducts by reduction with $LiAlH_4$ and can be readily separated from the virtually enantiomerically pure alcohols **IV** by chromatography. The analogous Diels-Alder reaction of acrylate **27** with 1,3-butadiene in the presence of $TiCl_4$ (molar ratio 1 : 4 : 1.4, 112 h at −8 °C in CH_2Cl_2) gave the (*R*)-3-cyclohexenyl carboxylate **28** in 98% yield with ≥95.6% diastereofacial selection[20].

Acrylates Derived from 3-Alkylborneols and -isoborneols: Further readily crystallizable auxiliary alcohols **I** such as **29** and **30** carry a *tert*-butyl shielding group attached to the bornanol skeleton by a chain of two carbon atoms[21]. In the $TiCl_2(OiPr)_2$-induced addition of the acrylates of **29** (*cis-exo*) and **30** (*cis-endo*) to cyclopentadiene the topological bias provided by **30** is significantly higher than that of **29** (Table 4).

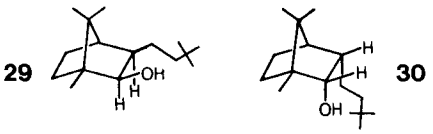

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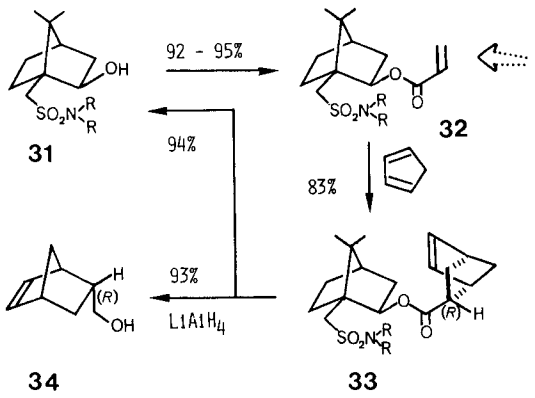
Table 4. Examples of the reaction of acrylates **II** derived from alcohols **I** (3-alkylisoborneols **29** and 3-alkylborneols **30**) with cyclopentadiene to give adducts **III** (for conditions, see text to Table 3).

Entry	I	Adduct III Yield [%]	*endo* [%]	C-5	d.e. [%]
1	**29**	75	89	*S*	66
2	**30**	89	92	*R*	94

3.2.2. *Acrylates Derived from Camphor-10-sulfonic Acid*

A new class of practical auxiliaries exploits the accessibility and crystalline nature of camphor-10-sulfonic acid derivatives.



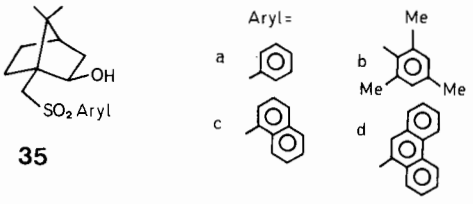
31 32 33 34

a, R = $CH(CH_3)_2$; **b**, R = cyclohexyl

Starting from (+)-camphor-10-sulfonyl chloride, successive amidation and reduction with L-Selectride[*] furnished the crystalline sulfonamides **31** in 57 to 68% overall yield. Their crystalline acrylates **32** undergo highly *endo*-selective $TiCl_2(OiPr)_2$-promoted additions to cyclopentadiene at −20 °C to give adducts **33** (97 to 98% yield) in 88 to 93% d.e.[22,23]. Intermediates and products were conveniently purified by crystallization which, for example, increased the diastereoisomeric purity of adduct **33a** from 88% to 99% d.e. The auxiliaries **31** were regenerated straightforwardly by reducing the adducts **33** with $LiAlH_4$ and subsequent separation from alcohol **34** by direct crystallization.

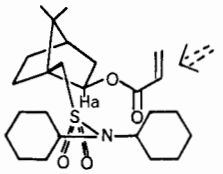
Similarly, a series of aryl sulfones **35** were readily prepared in three steps from camphor-10-sulfonic acid. Their usefulness as control groups in acrylate/cyclopentadiene

[*] L-Selectride = lithium tri-*sec*-butyl hydridoborate.

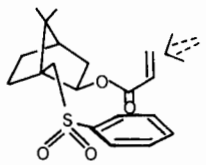


35

cycloadditions suffers from inferior π-face stereodifferentiation (64 to 69% d.e.) which outweighs other practical advantages[22,24].



32 b

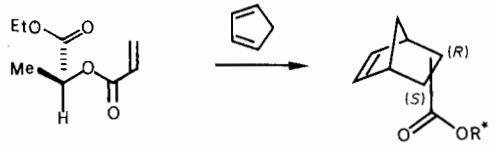


36

The superior topological differentiation of the sulfonamide-shielded acrylate **32b** is consistent with the results of an X-ray diffraction study[23]. In the crystal the uncomplexed acrylate adopts a strictly antiplanar arrangement of the $C_\alpha{=}C_\beta$ and C=O bonds, the latter of which lies ca. 30° out of the $C{-}H_a$ plane. As a result of sulfonamide conjugation, the nitrogen is planar, projecting the surface of one cyclohexane ring firmly on top of the olefinic bond. X-ray crystal structure analysis of the phenyl sulfone **36** indicates an almost identical acrylate conformation but less distinct shielding of its C_α-*re*-face, which is perpendicular to the sulfone-conjugated aryl group[24].

3.2.3. (S)-Ethyl-O-acryloyl Lactate

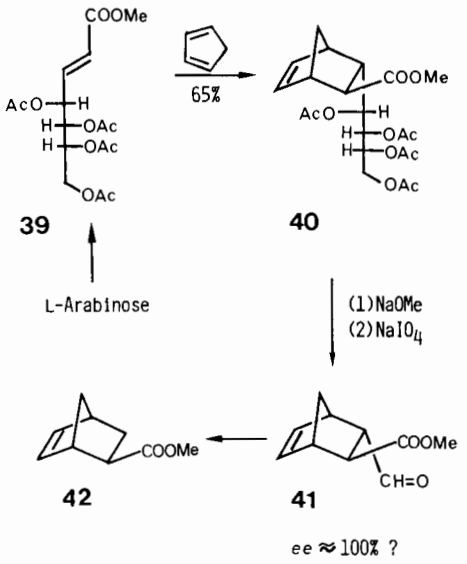
Interestingly, addition of the acrylate of (*S*)-ethyl lactate **37** to cyclopentadiene was reported to proceed with 86% C_α-*re*-face selection in the presence of $TiCl_4$, whereas the topicity was inverted (although to the extent of only 32% d.e.) by using $BF_3{\cdot}OEt_2$[25]. The (5*S*)-adduct **38** was purified by medium-pressure chromatography and saponified with retention of configuration.



37 38

3.2.4. α,β-Enoates with Chiral β-Substituents

High diastereotopic face differentiation has been claimed for the thermal (110°C!) addition of the enoate **39** derived from L-arabinose to cyclopentadiene, which after crystallization gave adduct **40** in 65% yield[26]. However, the composition of the mother liquor was not reported. Destructive cleavage of the sugar template gave aldehyde **41**, which was converted into ester **42**. The confusing chiroptic comparison of the rotation of **42** ($[\alpha]_D$ −10°, $CHCl_3$)

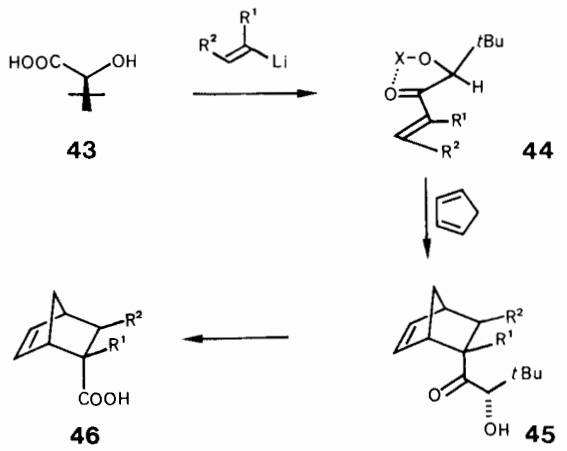


39 40 42 41

with a value published for enantiomerically impure **42** (e.e. ~25%) ($[\alpha]_D^{25}$ −10.2°, 95% EtOH, $c = 1.8$[27]) together with the lack of reliable HPLC or GC data suggests that this work should be evaluated with caution.

3.3. α,β-Unsaturated Ketones

A series of interesting features distinguishes conjugated α-hydroxy ketones **44** (X = H) and their enantiomers as chiral dienophiles[28,29]. Their preparation involves separation of acid **43** from its enantiomer followed by successive



43 44 46 45

Table 5. Examples for the reaction of α,β-unsaturated ketones **44** with cyclopentadiene to give adducts **45**; "*endo*" refers to the C=O group.

Entry	R^1	R^2	"Catalyst"	T [°C]	t [h]	Yield [%]	**45** *endo* [%]	d.e. [%]
1 **a**	H	H	—	−20	24	90	89	99
2 **a**	H	H	$ZnCl_2$	−43	1	95	94	>99
3 **b**	H	Me	—	+20	72	84	83	97
4 **b**	H	Me	$ZnCl_2$	−20	16	90	94	99
5 **c**	Me	H	$ZnCl_2$	0	24	~100	?	92

treatment with *n*BuLi and the appropriate vinyllithium reagent (molar ratio 1:2:1.5). Addition of cyclopentadiene occurs readily at −20°C even in the absence of a Lewis

acid (Table 5, entry 1) to give adduct **45a** with 99% diastereotopic π-face differentiation. This high selectivity undoubtedly derives from hydrogen bonding which locates the chiral center within a rigid five-membered ring. The bulky *tert*-butyl group enforces the C=O/C=C *syn*-conformation and directs the diene to the opposite enone face. The unusually high reaction rate can also be assigned to the hydrogen bond. In the presence of $ZnCl_2$, $BF_3 \cdot OEt_2$, or $Ti(OiPr)_4$, Diels-Alder additions to **44** proceed at even lower temperatures with improved *endo*- and π-face selectivities (entries 3, 4). Apparently, the dienophile system becomes more conformationally rigid and "activated" by chelation (**44**, X = metal), permitting efficient asymmetric Diels-Alder additions of less reactive dienophiles (entries 4, 5) and of various acyclic dienes (see Sections 7.6 and 7.7). However, the inevitable destruction of the valuable chiral auxiliary on oxidative removal (**45** → **46**) (successive reaction with iBu_2AlH, $NaIO_4$, Jones reagent) is an obvious shortcoming.

3.4. *N*-Acryloyl and *N*-Crotonyl Compounds

3.4.1. N-Acyloxazolidones

As an extension of elegant applications of chiral *N*-acryloyloxazolidones to asymmetric aldolizations and enolate alkylations[30], Diels-Alder reactions of the unsaturated secondary amides **47** and **49** were examined[31].

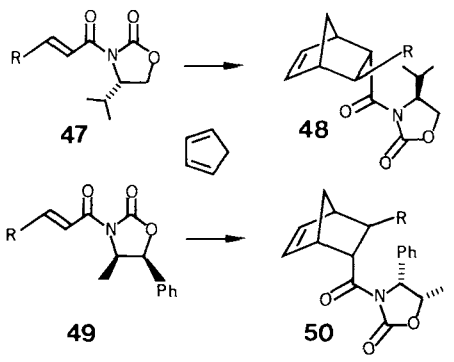
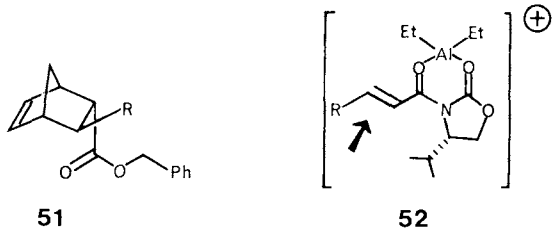


Table 6. Examples for the reaction of *N*-acyloxazolidones **47** and **49** with cyclopentadiene to give adducts **48** and **50**, respectively, in the presence of Et_2AlCl (1.4 mol per mol educt, −100 °C, 2 min). "*endo*" refers to the C=O group.

Entry	Educt	R	Adduct	Yield [%] [a]	*endo* [%]	d.e. [%] [b]	d.e. [%] [a]
1	**47**	H	**48**	81	>99	86	>98
2	**47**	Me	**48**	82	98	90	>98
3	**49**	H	**50**	82	99	90	>98
4	**49**	Me	**50**	88	98	96	>98

[a] Purified. [b] Crude.

Comparative studies of several Lewis acids revealed the essential advantage of using more than 1 equivalent of Et_2AlCl. Thus, Et_2AlCl-induced (1.4 equivalent) additions of the valinol derivatives **47** to cyclopentadiene were complete within 2 min at −100 °C and gave norbornenes **48** with 98 to 99% *endo*-selection and with 86 to 90% diastereofacial differentiation[31]. Inverse π-face topicity was displayed with similar efficacy by the norephedrine-derived dienophiles **49**. After recrystallization or chromatography, the resulting cycloadducts **48** and **50** were obtained in 81 to 88% yield and ≥98% d.e. Nondestructive cleavage of the oxazolidine auxiliaries from the adducts **48** and **50** by "transesterification" with lithium benzyloxide furnished the benzyl esters **51** or their enantiomers. The influence



exerted by Et_2AlCl on the Diels-Alder additions of dienophiles **47** is most plausibly ascribed to the intermediacy of the bidentate complex **52** which exhibits C=C/C=O-*syn*-planarity. The electron deficiency and rigid structure of **52** account for the high reactivity and good π-face differentiation. Even less reactive acyclic dienes add smoothly to such chelated dienophiles at temperatures ≤ −30 °C (6 h); interestingly, in this case the (*S*)-benzyl derivatives **53** (Table 7) displayed much higher diastereoselectivity than the isopropyl derivatives **47**.

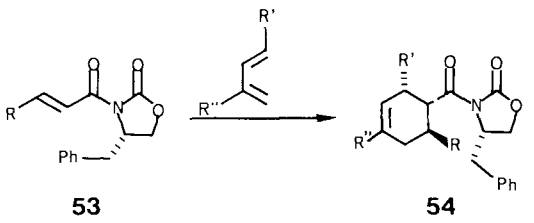


Table 7. Examples for the reaction of the *N*-acryloyloxazolidones **53** with butadienes in the presence of Et_2AlCl (1.4 mol per mol **53**, −100 to −30 °C) to give the adducts **54**.

Entry	R	R'	R''	Yield [%] [a]	d.e. [%] [b]	d.e. [%] [a]
1	H	H	Me	85	90	>98
2	H	Me	H	84	>99	>98
3	Me	H	Me	83	88	>98
4	Me	Me	H	77	90	>98

[a] Purified. [b] Crude.

3.4.2. N-Acylsultams Derived from Camphor

Exceptional dienophile "activation" coupled with the practical advantages of camphor-10-sulfonamides distinguish the sultam auxiliary **55**[32]. The highly crystalline sultam is available in two to three convenient synthetic operations from camphor-10-sulfonyl chloride in 76% overall yield. Efficient *N*-acylation furnished the crystalline, stable *N*-acryloyl and *N*-crotonyl derivatives **56** and **57**. $EtAlCl_2$-promoted Diels-Alder addition of butadiene to **56** proceeded readily at −78 °C to give the (5*S*)-adduct **58** in 93% yield with 97% π-face selection (Table 8, entry 1). In the presence of $EtAlCl_2$ or $TiCl_4$, cyclopentadiene added

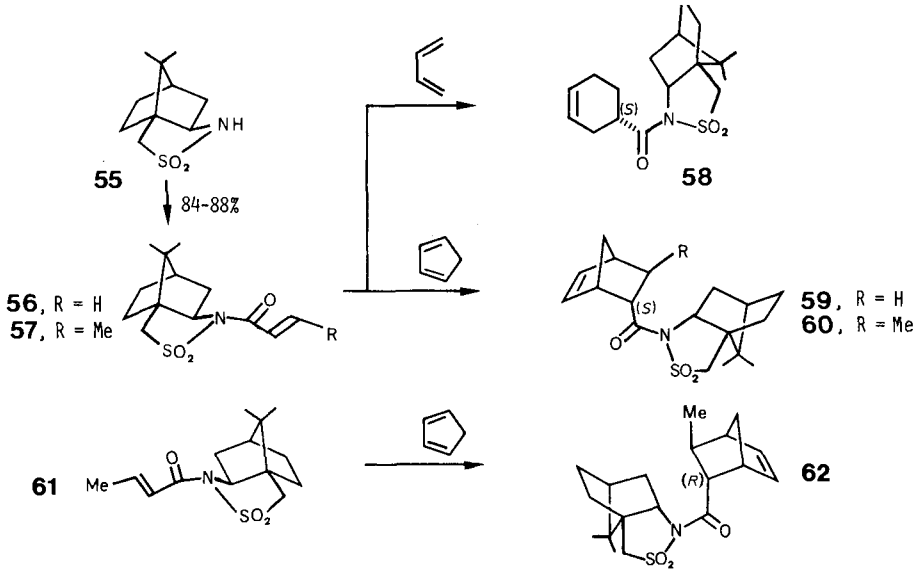
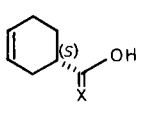


Table 8. Examples for the reaction of *N*-acryloylsultams **56**, **57** and **61** to give the adducts **58**–**60** and **62**; "*endo*" refers to the C=O group.

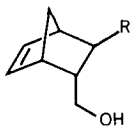
Entry	Educt	Conditions [a]	Adduct	Yield [%] [b]	*endo* [%]	d.e. [%] [c]	d.e. [%] [d]
1	**56**	A	**58**	81	—	97	99
2	**56**	B	**59**	84	99.5	95	99
3	**57**	C	**60**	83	99	93	99
4	**57**	A	**60**	—	96	98	—
5	**61**	A	**62**	—	98	94	—

[a] A: $EtAlCl_2$ (1.5 mol per mol educt), CH_2Cl_2, −78°C, 18 h. B: $EtAlCl_2$ (1.5 mol per mol educt), EtCl, −130°C, 6 h. C: $TiCl_4$ (0.5 mol per mol educt), CH_2Cl_2, −78°C, 1 h. [b] Recrystallized adducts, yields relative to dienophile. [c] Crude. [d] Recrystallized adducts, ≈ 100% *endo*.

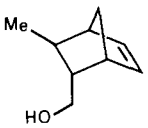
smoothly to **56** even at −130°C and to the less reactive **57** at −78°C (entries 2, 3, 4). Under these conditions, 96–99.5% *endo* and 93–98% π-face selectivities were achieved. Moreover, each of the butadiene and cyclopentadiene adducts (**58**, **59**, **60**) was obtained virtually pure in 82 to 84% yield after simple recrystallization. The sense of asymmetric induction could be easily reversed (**61** → **62**, entry 5) by exploiting the ready availability of (−)-camphor.



63, X = H_2
67, X = O

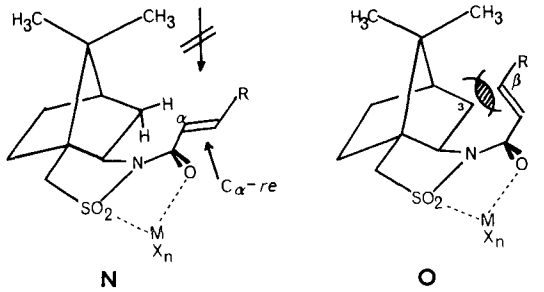


64, R = H
65, R = Me



66

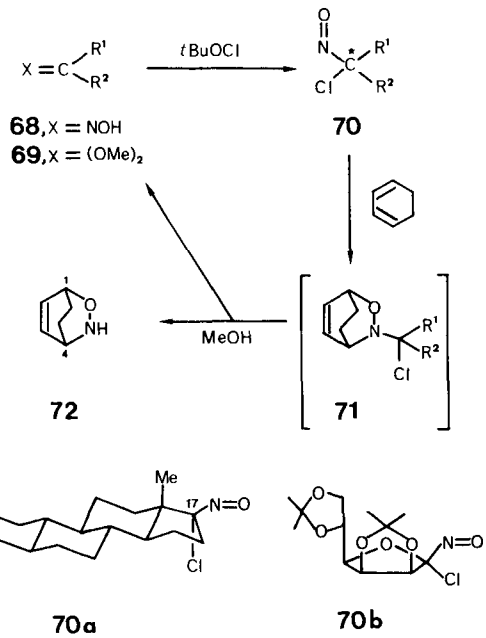
Reduction of the cycloadducts **58**—**60** with $LiAlH_4$ refurnished the sultam **55** (or its enantiomer from **62**) in 89—95% yield after crystallization and gave the pure alcohols **63** to **66** in 89—95% yield on subsequent kugelrohr distillation. Alternatively, saponification of adduct **58** with LiOH gave the acid **67** *without* epimerization. It appears that the remarkable Diels-Alder reactivity of the otherwise stable *N*-acylsultams **56** and **57** is based on chelation of the SO_2 and C=O groups. The postulated chelate would be locked into conformation **N** (**O** then being excluded), which directs the diene to the less hindered bottom face (C_α-*re*).



N **O**

3.5. α-Chloronitroso Dienophiles

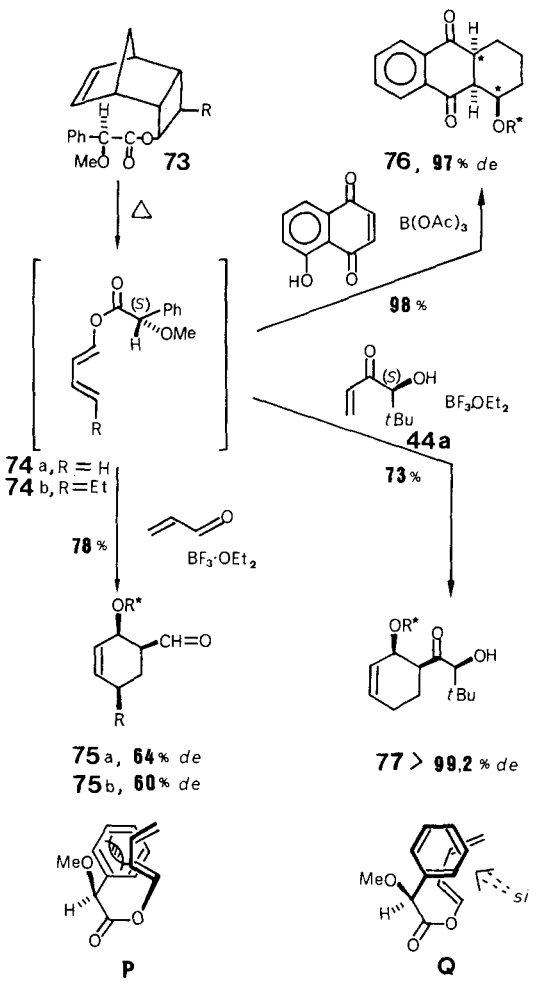
An original approach to the enantiomerically pure oxazine derivatives **72** (>95% e.e.) involves hetero Diels-



Alder additions of 1,3-cyclohexadiene to chloronitroso compounds **70**, readily prepared from oximes **68**. Methanolysis of the non-isolated adducts **71** in situ furnished acetals **69** and oxazines **72**. Thus, (1*R*,4*S*)-**72** was obtained from the steroid derivative **70a** (with 72% regeneration of the C-17 ketone)[33]; the chloronitroso ether **70b** derived from mannonolactone reacted considerably faster with cyclohexadiene to give (after removal of the inexpensive auxiliary reagent) (1*S*,4*R*)-**72**[34].

4. Chiral Dienes

Asymmetric Diels-Alder reactions of dienes substituted with a removable chiral moiety to prochiral dienophiles have been less extensively studied. Thermal additions of 1,3-dienol ethers derived from sugars suffer from low *endo*-selectivity[35]. So far, disappointing inductions have been achieved in Diels-Alder reactions accelerated by high pressure, as exemplified by the additions of chiral 2,4-pentadienoates to *p*-benzoquinone; at 15 kbar the expected adducts were obtained in 58—98% yield, but in humble (2—50% d.e.) stereofacial selectivity[36]. The general advantage of Lewis-acid coordination is again illustrated by the [4+2]-addition of the dienes **74** derived from (*S*)-*O*-methylmandelic acid (readily accessible from **73**) to acrolein in the presence of $BF_3 \cdot OEt_2$ (0.15 mol per mol **74**, toluene, −20°C, 48 h) which gave adducts **75** in 98% yield with 60 to 64% diastereofacial differentiation[37].



Virtually complete asymmetric induction was observed on addition of **74a** to juglone [$B(OAc)_3$ 1.6 mol per mol **74a**, $CHCl_3$, 0→20°C], giving **76** in 98% yield and >97% d.e. These findings have been rationalized in terms of a binding diene/aryl π-orbital overlap. In this π-stacking model, methoxy/diene repulsion disfavors conformer **P** over conformer **Q**, which undergoes preferential dienophile addition opposite to the phenyl-shielded diene-face. The destruction of the chiral auxiliary on hydrogenolysis constitutes a practical disadvantage.

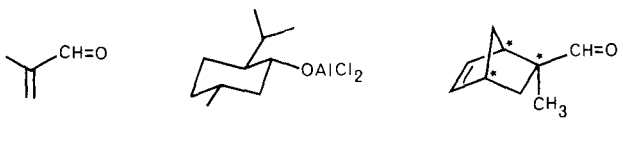
The cooperative effect of chiral auxiliaries at the diene *and* dienophile units is exemplified by the double diastereoface selective addition **74a** + **44a** → **77** (99% d.e.). On analogous addition of the enantiomer of **74a** to **44a**, the dienophile face-directing efficiency exceeds that of the diene, leading to the adduct **77** (R* = (*R*)-*O*-methylmandeloyl) in 94% d.e.[29].

5. Chiral Catalysts

At first sight, the use of a chiral catalyst appears to be the potentially most attractive method to achieve asymmetric Diels-Alder reactions of prochiral dienes and dienophiles. Compared to the stoichiometric use of a covalently attached prosthetic group, two synthetic steps would be avoided.

5.1. Chiral Alkyloxy-Substituted Lewis Acids

The addition of cyclopentadiene to methacrolein **78** → **80** catalyzed by (−)-menthyloxyaluminum dichloride **79** is so far the *only* reported example that affords greater than 60% asymmetric induction[38]. Although when we attempted to reproduce this work, we obtained no more than 55% enantiomerically pure adduct **80**, other [4+2]-cycloadditions of cyclopentadiene to diverse dienophiles using various chiral Lewis acids were far less π-face selective[39].



78 **79** **80**

5.2. Interaction between Chiral Catalyst and Chiral Diene Auxiliary Reagent

Traces (0.5 to 5 mol%) of soluble europium complexes catalyze hetero Diels-Alder reactions of silyloxydienes to arylaldehydes. Thus, dienes **81** reacted smoothly with benzaldehyde at room temperature in a highly *endo*-selective manner to give exclusively *cis*-substituted dihydropyrans **82**, which on acid-promoted elimination furnished dihydropyrones **83** in good overall yield. Using $Eu(hfc)_3$ as a chiral catalyst (Table 9), (*R*)-**83** was obtained from the prochiral diene **81a** in only moderate e.e. (42%), but in an impressive 86% e.e. from the chiral diene **81b**[40]. Interestingly, the interactivity of diene auxiliary reagent and catalyst

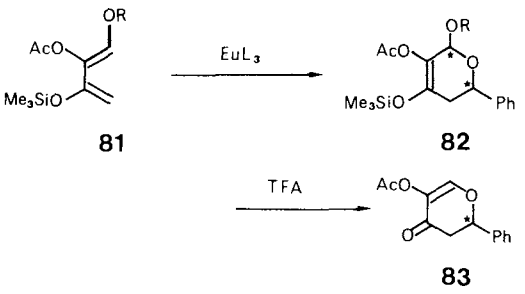


Table 9. Examples for the reaction of siloxydienes **81** with benzaldehyde to give adducts **83** in the presence of europium compounds.

Entry		R	EuL_3 [a]	C-2	e.e. [%]
1	**a**	*t*Bu	$Eu(hfc)_3$	*R*	42
2	**b**	(3*R*)-menthyl	$Eu(hfc)_3$	*R*	86
3	**c**	(3*S*)-menthyl	$Eu(hfc)_3$	*R*	18
4	**b**	(3*R*)-menthyl	$Eu(fod)_3$	*S*	10

is maximal when the individual π-facial biases are of opposite sense (entries 1—4).

6. Intramolecular Diels-Alder Reactions

Because of their high regio- and diastereoselectivity[41], intramolecular cycloadditions have been widely used for the efficient synthesis of numerous cyclic molecules. Absolute configurational control by means of removable chiral auxiliaries is, however, at a comparatively early stage.

6.1. Chiral Dienophile Auxiliary Groups

Not surprisingly, concepts developed successfully for bimolecular asymmetric Diels-Alder reactions have been applied to intramolecular versions such as the transformations **84** → **85** and **84** → **86**. Dienophile π-face shielding by the 8-phenylmenthyl moiety proved to be less efficient (Table 10, entries 1, 2)[42] than that by the *N*-oxazolidone groups (entries 3—6)[43]. Moreover, the secondary amides **84c** to **84f** cyclized with superior *endo*-selectivity, and products **85** or **86** were obtained in good yields and >99% d.e. after chromatography.

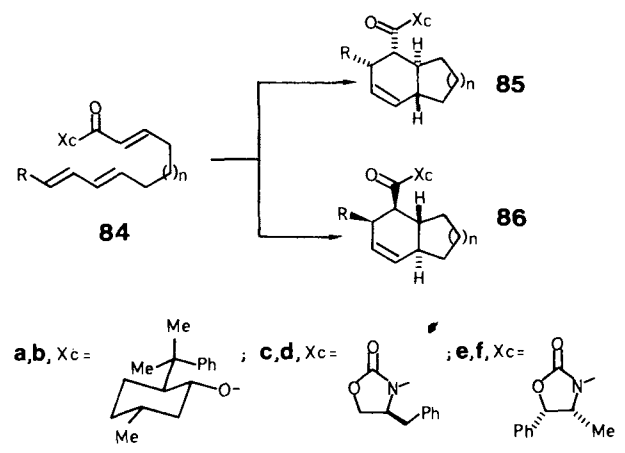


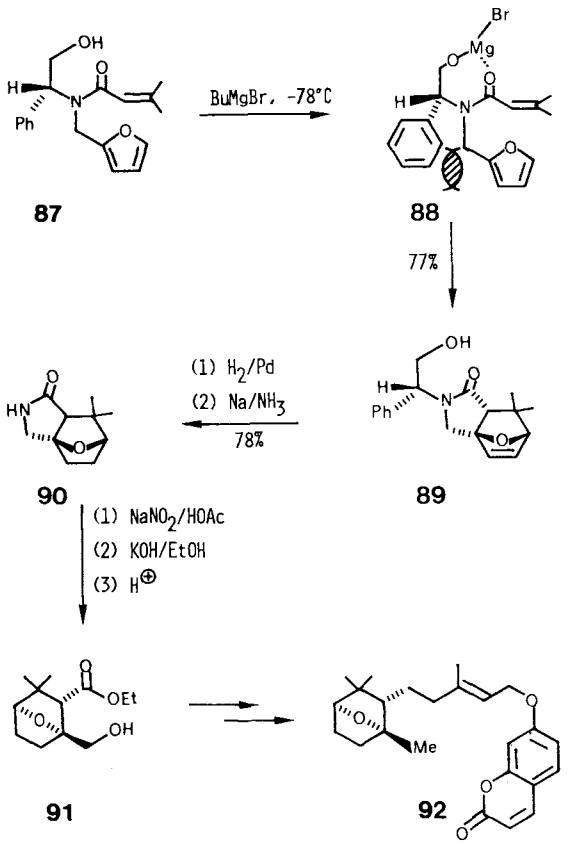
Table 10. Examples for the intramolecular reaction of polyenes **84** to give the bicyclic adducts **85** and **86**.

Entry		n	R	Conditions [a]	Yield [%]	**85** : **86**
1	**a**	1	H	A	72 [b]	86 : 14
2	**b**	1	*i*Pr	B	61 [b]	67 : 33
3	**c**	1	H	C	73 [c]	95 : 5
4	**d**	2	H	C	88 [c]	97 : 3
5	**e**	1	H	C	70 [c]	15 : 85
6	**f**	2	H	C	70 [c]	6 : 94

[a] A: [(−)-bornyloxy]$AlCl_2$ (1.6 mol per mol **84**), 8°C, 336 h; B: [(−)-bornyloxy]$AlCl_2$ (1.8 mol per mol **84**), 23°C, 92 h; C: Me_2AlCl (1.4 mol per mol **84**), −30°C, 5 h. [b] Overall yield **85** + **86**. [c] Yield of >99% diastereomerically pure major product.

6.2. Chiral Auxiliary Reagents as Part of the Bridge

An interesting example is the thermal cycloaddition of magnesium salt **88** to give adduct **89** in 76% d.e.[44]. In contrast, analogous addition of free **87** proceeded slower and without π-face selectivity. It thus appears that chelation of the dienophile carbonyl group with the bridge-residing control moiety accelerates the rate of addition and provides the essential conformational rigidity of **88**. Repulsion between the α-furyl methylene group and the phenyl ring is minimized in the transition state which leads to **89**.



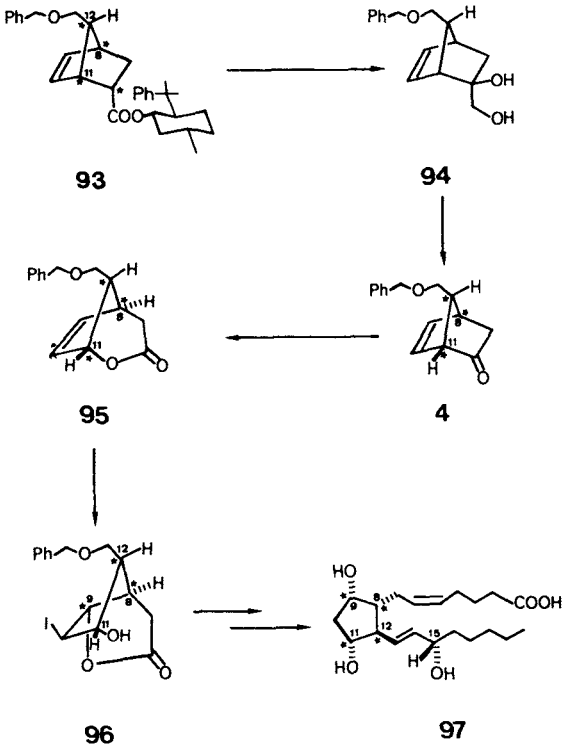
After hydrogenation of the olefinic bond in **89**, the chiral auxiliary reagent was destructively cleaved by reduction to give lactam **90**, which was converted into **92**, the enantiomer of naturally occurring farnesiferol-C.

7. Applications in Organic Synthesis

Natural product synthesis has often led to important methodological advances by provoking either the discovery of new methods or the rigorous testing and refining of existing ones. This holds also for the asymmetric Diels-Alder reaction as outlined below.

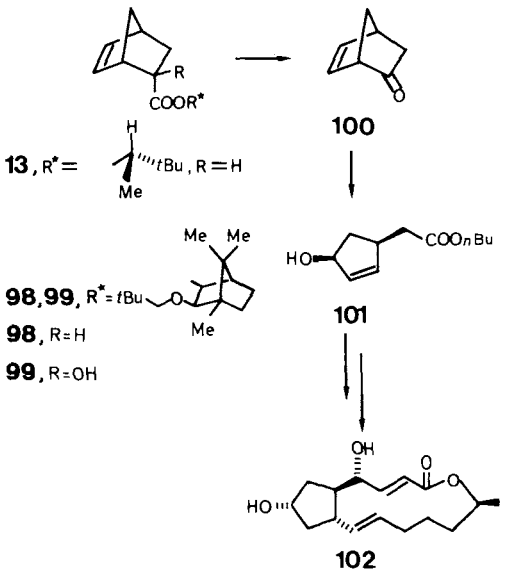
7.1. Prostaglandins

In the course of attempts to synthesize the enantiomerically pure prostaglandin **97** the 8-phenylmenthyl auxiliary reagent has been developed. Thus, the addition **1b** + **2b** → (1*S*)-**3b** ≡ **93** (Section 2) simultaneously generated three enantiomerically enriched centers which correspond to the carbon atoms C-8, C-11, and C-12 of the prostaglandin target molecule. The correct oxidation state of C-11 was then established by Baeyer-Villiger oxidation **94** → **95**, and the center C-9 was induced by center C-8 during the transformation **95** → **96**. Crystallization provided enantiomerically pure **96**[4], which was converted into **97** by established procedures.



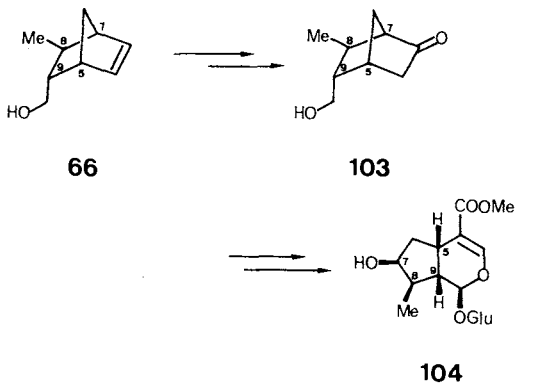
7.2. (+)-Brefeldin-A

One synthesis of (+)-brefeldin-A **102** started from the diastereomerically enriched cycloadduct **13**[16]. Degradation of this furnished norbornenone **100** (80–85% e.e.), which was transformed into crude **102**. The final product was purified by HPLC and crystallization to afford ca. 100% e.e. Alternatively, the cycloadduct **98** gave on hydroxylation and crystallization diastereomerically pure **99**, which on degradation refurnished the auxiliary reagent (88%) and afforded **100** in >99% e.e.[45].



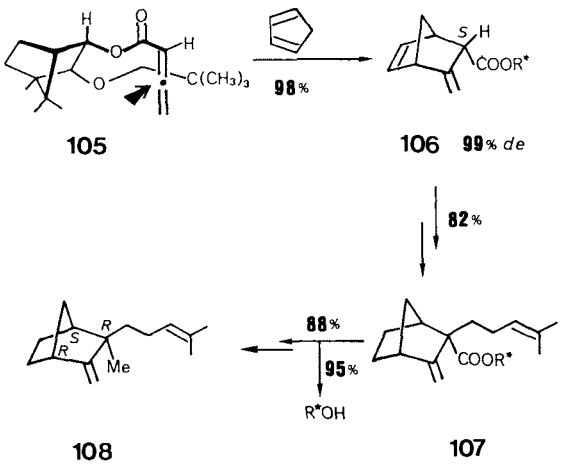
7.3. Loganin

The synthetic potential of enantiomerically pure cyclopentadiene-Diels-Alder adducts is further exemplified by the synthesis of (±)-loganin **104** from (±)-**66**[46]. Accordingly, the asymmetric [4+2]-additions **47** → **48**[31] and **61** → **62**[32] generate the correct relative and absolute configuration of the centers C-5, C-7, C-8, and C-9 of the loganin precursor **66**.



7.4. (−)-β-Santalene

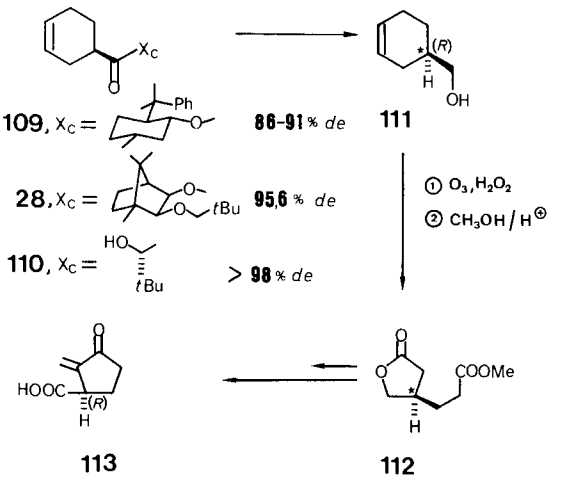
A synthesis of the sandalwood constituent (−)-β-santalene **108** (ca. 100% e.e.)[47] relies on the $TiCl_2(OiPr)_2$-pro-



moted cycloaddition of the chiral allenic ester **105** to cyclopentadiene (−20 °C, 6 h) which gave adduct **106** in 98% yield with 98% *endo*-selectively and 99% d.e. Subsequently, **106** was transformed into **108** following a protocol previously reported for the synthesis of racemic β-santalene[48]. Notably, approximately 100% diastereomerically pure intermediate **107** was obtained after crystallization in 82% yield (from crude **106**).

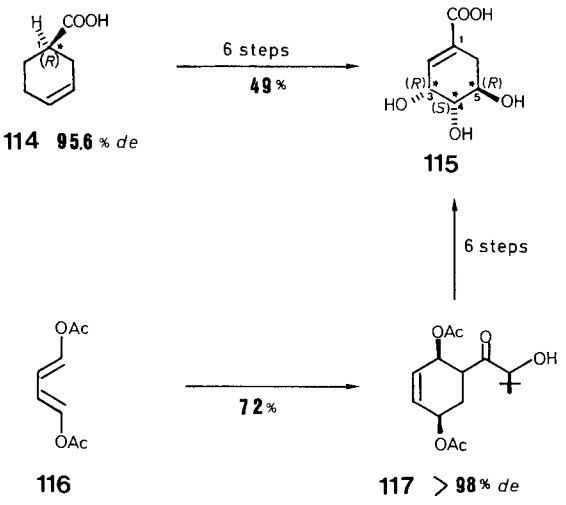
7.5. (−)-Sarkomycin

For a possible synthesis of (*R*)-(−)-sarkomycin **113**[49] the butadiene cycloadducts **109**[49], **28**[20], and **110**[29] furnish the (*R*)-precursor **111** in high e.e.



7.6. (−)-Shikimic Acid

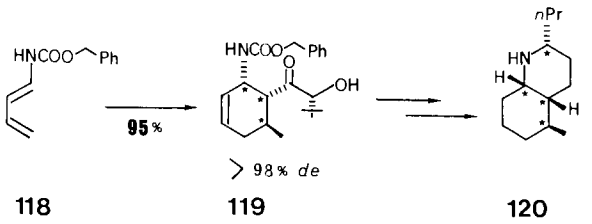
The (*R*)-carboxylic acid **114**, accessible from adduct **28** in 83% yield by reduction with $LiAlH_4$ and subsequent oxidation of **111** with Jones reagent[20], is a potential precursor of (−)-shikimic acid **115**[50]. Another route to (−)-**115**



involves $BF_3 \cdot OEt_2$-promoted [4+2]-addition of diene **116** to **44a**, $X = R^1 = R^2 = H$ (−43 °C, 5 h) giving **117** in 98% d.e.[29].

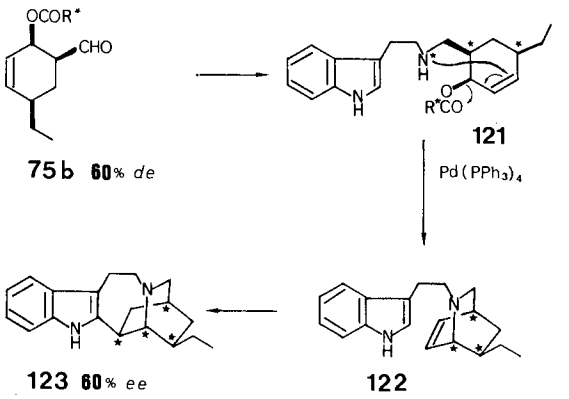
7.7. (+)-Pumiliotoxin-C

Addition of diene **118** to the enantiomer of **44b**, $X = R^1 = H$, $R^2 = Me$, ($BF_3 \cdot OEt_2$, toluene, −78 °C, 0.5 h) afforded adduct **119** (>98% d.e.), which was transformed into the pure enantiomer **120** of naturally occurring (−)-pumiliotoxin-C[29].



7.8. (+)-Ibogamine

The goal of synthesizing (+)-ibogamine **123** has initiated the study of asymmetric Diels-Alder additions of chiral dienes[51]. Adduct **75b** (60% d.e.) gave on reductive



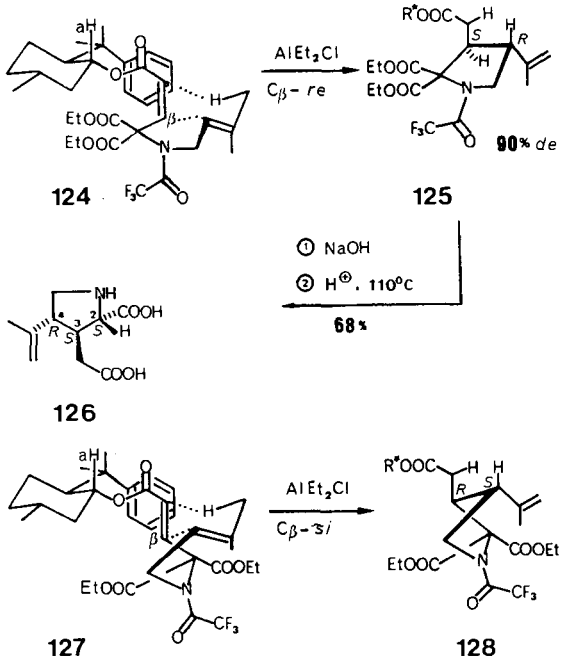
amination with tryptophan the secondary amine **121**. Subsequent Pd^0-catalyzed allylic displacement of the *O*-methylmandeloyl auxiliary yielded quinuclidine **122**, which was cyclized to give enantiomerically enriched **123**.

8. Asymmetric Ene-Reactions

The mechanistic similarity between the Diels-Alder cycloaddition and the ene-process[52] leads one to expect the applicability of analogous π-face differentiation concepts.

8.1. Synthesis of (+)-α-Allokainic Acid

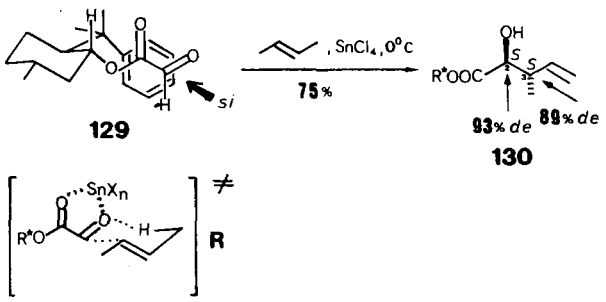
In accord with this postulate, the total synthesis of (+)-α-allokainic acid **126** features an Me_2AlCl-mediated, intramolecular ene-reaction **124** → **125** which controls the relative (100%) and the absolute (90% d.e.) configuration of the developing centers at C-3 and C-4[53]. Subsequent saponification, decarboxylation, and crystallization yielded the pure natural product **126** (ca. 100% e.e.) and refurnished the auxiliary reagent (−)-8-phenylmenthol. The strong enophile face-directing influence of the control group has been explained by an antiplanar $C_\alpha = C_\beta / C = O$



and a synperiplanar C=O/C–H_a enoate conformation where the phenyl ring shields the C_β-*si*-face. Evidence provided by ^{1}H-NMR spectroscopy indicates that this shielding occurs even in the absence of the Lewis acid. Coordination with R_2AlCl, however, was found to be essential for the high reaction rate as well as for the diastereofacial- and *exo*-selectivity. As expected, the sense of asymmetric induction could be reversed (78% d.e.) by using the same control group but changing the enoate geometry (**127** → **128**) which led to pure (−)-α-allokainic acid. The topological considerations and practical problems encountered here prompted the careful reinvestigation of the phenylmenthyl-directed Diels-Alder reaction[11], which has stimulated the discovery of more practical and efficient chiral auxiliaries[18,22,23,32].

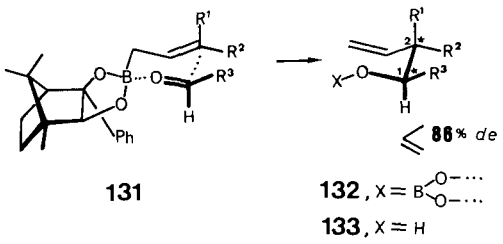
8.2. Chiral Glyoxalates

Similar enophile facial selection occurs in the $SnCl_4$-promoted addition of *trans*-2-butene to phenylmenthyl glyoxalate **129** → **130**[54]. The excellent control over the (2*S*)-configuration in **130** was attributed to a selective *re*-face shielding of the aldehyde C=O bond which is *syn* to that of the ester carbonyl. This *syn*-relation might result from chelation as depicted in transition state **R**. The preferred *exo*-mode of addition governs the relative configuration C-2/C-3 in **130**.



8.3. Additions of Allylboronates to Aldehydes

Another asymmetric ene-type process, the addition of allylboronates to aldehydes (**131** → **132**)[55] involves the transfer of boron from carbon to oxygen and thus represents a version of the "metallo-ene reaction"[20]. The chiral auxiliary is attached to the boron atom and regenerated from the adduct **132** by B/O-cleavage with nitrilotriethanol, which also affords the free homoallylic alcohols **133**.



This first use of a camphor glycol as a chirality directing group provides ene-face differentiations (C-1) of between 52 and 89% d.e. The preferred "*exo*"-mode of addition controls the relative topicity C-1/C-2 (86—94%).

8.4. Addendum

A crystal structure analysis of the 1 : 1 complex of ethyl (*S*)-acryloyllactate **37** with $TiCl_4$ indicates chelation of both ester carbonyl oxygen atoms by titanium and a synplanar C=O/C_α=C_β conformation. The selective blocking of the C_α-*re*-face is consistent with the results observed for the $TiCl_4$-assisted addition **37** → (5*R*)-**38** (Section 3.2.3). In the presence of $BF_3 \cdot OEt_2$ or $EtAlCl_2$ the addition **37** → (5*S*)-**38** (≤ 56% d.e.) proceeds with the opposite topology and is in accord with a reactive conformation **D** (Section 3.1)[56].

9. Conclusions and Outlook

The asymmetric Diels-Alder reaction is a powerful tool for the synthesis of enantiomerically pure, complex molecules. Regenerable chiral dienophile auxiliaries in combination with a Lewis acid provide a number of advantages such as conformational rigidity, acceleration in rate, improved *endo*-selectivity, and ease of purification by chromatography or crystallization. The capacity of chiral auxiliaries to override the influence of pre-existing chiral centers in the substrate(s) simplifies stereorational design in synthesis. The relatively unexplored areas of diene auxiliaries and intramolecular versions are certain to receive more attention. Progress in the development of chiral catalysts may be spurred on either by new structural information on coordinated dienophiles and dienes or by purely empirical discoveries. The still modest performance of the high-pressure methodology might benefit from technological advances. The potential of the same π-face differentiating principles in absolute acyclic stereoselection, as exemplified here by the ene process, applies also to other classes of reaction.

It is clear that the field covered by this review has entered the stage of practical use in organic synthesis which will put its scope and limits to the test in the near future.

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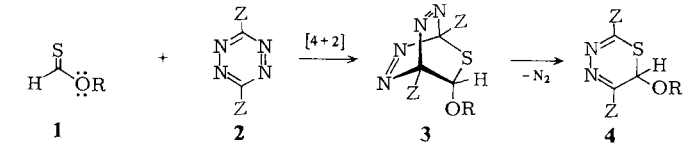
Donor-Substituted Thiocarbonyl Functions as Heterodienophiles in [4+2]-Cycloadditions with Inverse Electron Demand**

By *Gunther Seitz**, *Rolf Mohr*, *Wolfgang Overheu*, *Rudolf Allmann*, and *Michael Nagel*

Because of their extraordinary reactivity in both bimolecular[1-3] and intramolecular[2] [4+2]-cycloadditions, thiocarbonyl dienophiles have been the subject of wide interest in recent years. This synthesis, which for substituted thiopyran systems proceeds under extremely mild conditions, was nevertheless essentially limited to reactions of electron-rich dienes with acceptor-substituted thiocarbonyl dienophiles[1].

Our results now show, for the first time, that thiocarbonyl compounds also function as excellent heterodienophiles in Diels-Alder cycloadditions with inverse electron demand[4], provided the donor groups are sufficiently activated. Thiocarbonyl compounds react smoothly with the *s-cis*-fixed azine system in the tetrazines **2**, which because of the trifluoromethyl or ester groups are extremely electron

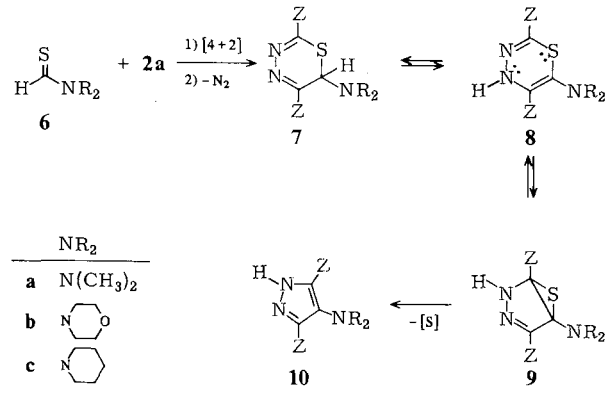


1 **2** **3** **4**

a, R = C_2H_5 **a**, Z = CF_3 **4**: Z = CF_3
b, R = C_3H_7 **b**, Z = CO_2CH_3 **5**: Z = CO_2CH_3

deficient, to afford the novel 6*H*-1,3,4-thiadiazines **4**, **5**, **7**, and **15**. Depending on the substitution pattern, the products can fragment more or less easily to pyrazoles and sulfur[5].

In the first step of the reaction, e.g. of the thioformate esters **1** with the tetrazines **2**, the electron-rich thiocarbonyl function adds to the acceptor-substituted diazadiene system via [4+2]-cycloaddition. The non-isolable bicyclic Diels-Alder adduct **3** is formed, whose considerable ring strain facilitates rapid elimination of nitrogen via a [4+2]-cycloreversion[6] in a fast follow-up reaction. The chiral, lemon-yellow 6*H*-1,3,4-thiadiazines **4** and **5**, which are, respectively, liquids distillable in vacuo and crystalline compounds, are thereby produced in 50—70% yield[7].

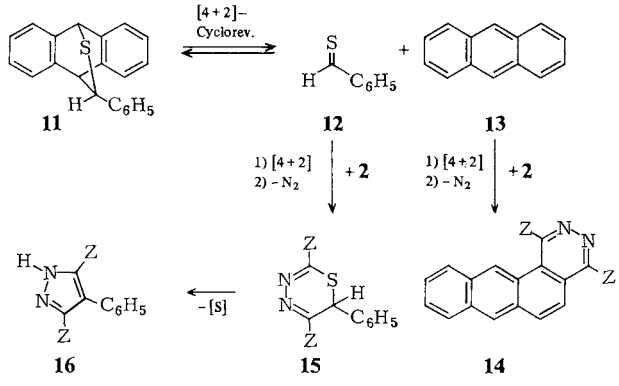


6 **7** **8**

a $N(CH_3)_2$
b
c

10 **9**

With the thioformamides **6** as heterodienophiles, the pharmacologically interesting 4-aminopyrazoles **10** are isolated as the sole products of the reaction[7]. The results of a preliminary crystal structure analysis[8] of the compound obtained from **6a** and **2a** are consistent with the constitution **10a**. 6*H*-1,3,4-Thiadiazines of type **7** may primarily be formed as intermediates which exist in equilibrium with the higher energy 4*H*-tautomers **8**. As cyclic 8π systems, these undergo valence isomerization to the bicycles **9**; subsequent elimination of sulfur leads to the pyrazoles **10** in ca. 20% yield[9].



11 **12** **13**

16 **15** **14**

Thioaldehydes can also undergo "inverse" [4+2]-cycloadditions with **2**. As we discovered, the thiobenzaldehyde **12**, generated in a retro Diels-Alder reaction from the adduct **11**[2], can be trapped by **2**. By analogy to the reaction sequence **7**→**10**, a ring contraction of the 6*H*-1,3,4-thiadiazines **15** to the 4-phenylpyrazoles **16** occurs. The structure of **16b** is based on independent synthesis ([3+2]-cycloaddition of methyl diazoacetate to methyl phenylpropiolate)[10]. Interestingly, the tetrazines **2** react under the necessarily drastic conditions of the [4+2]-cycloreversion of **11** also with anthracene **13** to give naphthophthalazines **14**, and hence a total of three [4+2]-cycloadditions compete with each other in the reaction mixture. With **2a** as educt, predominantly **16a** is formed (63%, m.p. = 160°C; **14a**: 4%, m.p. = 210°C); with **2b**, **14b** is preferentially formed (31%, m.p. = 191°C; **16b**: 11%, m.p. = 151°C).

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Procedure

2a, **b** (5 mmol) and **1a**, **b** (5 mmol) are dissolved in 30 mL anhydrous toluene and the mixture is heated until the red color of **2** disappears. The products **4** (yellow oils) are distilled in vacuo; the crystalline products **5** are purified by recrystallization from *n*-hexane/cyclohexane (1:1). In order to obtain **10a**–**c**, **2a** is allowed to react analogously with **6a**–**c** at room temperature in 30 mL CCl_4; after preparative thin-layer chromatography on silica gel (eluent benzene), the products are recrystallized from *n*-hexane.

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[7] For example, **4b**: Yield 71%, b.p. = 40°C/0.2 torr, UV (CH_2Cl_2): λ_{max} = 278 (lg ε = 3.4), MS (CI with isobutane): *m/z* 295 ($M^{\oplus}+1$, 100%).—**5a**: Yield 50%; m.p. = 90°C, UV (CH_2Cl_2): λ_{max} = 296 nm (lg ε = 3.4); MS (CI with isobutane): *m/z* 261 ($M^{\oplus}+1$, 100%).—**10a**: Yield 17%, m.p. = 98°C (*n*-hexane); IR (KBr): ν = 3180 (NH), 1150 cm^{-1} (CF_3); MS: *m/z* 247 ($M^{\oplus}$, 36%), 246 (100%).
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Synthesis of a Stable Aminosilanol and a Lithium Aminosilanolate with Cubane Structure**

By *Onno Graalmann, Uwe Klingebiel*, William Clegg, Martin Haase,* and *George M. Sheldrick*

Although chloroalcohols of type $R_2C(Cl)OH$ and aminoalcohols of type $R_2C(NH_2)OH$ are, to our knowledge, unknown, we recently succeeded in preparing stable chlorosilanols[1] by reaction of silanediols with PCl_5 accompanied by formation of HCl and $POCl_3$, despite their existence being considered highly improbable because of easy loss of HCl[2]. We now report the synthesis of a stable aminosilanol **2**[3], which is formed in a simple reaction on treatment of di-*tert*-butylchlorosilanol **1**[1] with ammonia.

1 $tBu_2Si(Cl)OH \xrightarrow[-NH_4Cl]{+2NH_3} tBu_2Si(NH_2)OH$ **2**

A condensation involving inter- or intramolecular NH_3- or H_2O-cleavage was not observed. **2** reacts with butyllithium in the molar ratio 1:1 with formation of a lithium aminosilanolate **3**[4] and butane.

2 $\xrightarrow[-BuH]{+NuLi} tBu_2Si(NH_2)OLi$ **3**

A primary metalation of the amino group can, according to the ^{1}H-NMR spectrum, be ruled out. Because of the voluminous *tert*-butyl groups, **3** is not very sensitive to hydrolysis. According to its EI mass spectrum, **3** is tetrameric in the gas phase. In the ^{29}Si-NMR spectrum of **3** the resonance signal is, as expected, shifted upfield compared to the corresponding signal of **2**.

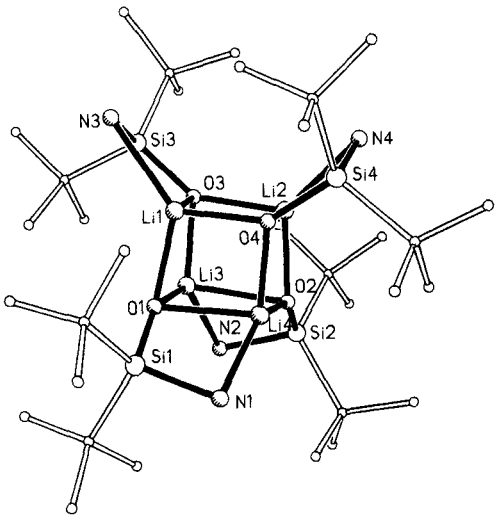

Fig. 1. Molecular structure of **3** in the crystal [8].

In the solid state, **3** is tetrameric and has a pseudo-cubane structure[5–8]. The distorted cubic cluster is made up of interpenetrating Li_4 and O_4 tetrahedra (bond lengths [pm]: Li–Li 255–262, O–O 291–312, Li–O 191–211; bond angles [°]: O–Li–O 93.6–101.5, Li–O–Li 78.6–85.6). Each Li atom achieves its usual fourfold coordination by the formation of a Li–N bond (220–230 pm) with the nitrogen of the aminosilanolate. The particularly long Si–N bonds (178–180 pm), the indicated positions of the hydrogen atoms on the nitrogen[8], and the upfield shift of the NH_2 resonances in the ^{1}H-NMR spectrum of **3** compared to those of **2** point to tetrahedral nitrogen coordination. The two sorts of *tert*-butyl groups found in the solid by a crystal structure investigation are equilibrated in solution. Temperature-dependent ^{1}H-NMR measurements down to −80°C in toluene showed only one resonance signal for the *tert*-butyl groups. It can therefore be concluded that no tetrameric structure is present in solution.

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(C_6H_6/C_6D_6, TMS int.): $\delta = 0.43$ (NH_2), 1.03 (*t*Bu), 2.28 (OH); ^{29}Si-NMR (C_6H_6/C_6D_6, TMS int.): $\delta = -3.84$.

[4] **3**: colorless solid; recrystallized from *n*-hexane; m.p. 214°C; MS (70 eV): *m/z* 667 (13%, $M^{\oplus} - t$Bu; ^{1}H-NMR (C_6H_6/C_6D_6, TMS int.): $\delta = 0.28$ (NH_2), 1.12 (*t*Bu); ^{13}C-NMR (C_6H_6/C_6D_6, TMS int.): $\delta = 20.57$ (*SiC*), 29.32 ($SiCC_3$); ^{29}Si-NMR (C_6H_6/C_6D_6, TMS int.): $\delta = -10.08$.

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Thermospray Mass Spectrometry of Diquaternary Ammonium Salts**

By *Günter Schmelzeisen-Redeker, Ulrich Giessmann,* and *Franz-Wilhelm Röllgen**

Molecular weight determination and identification of diquaternary salts is hindered by difficulties in obtaining analytically useful mass spectra. Recent applications of secondary ion, fast atom-bombardment and laser desorption mass spectrometry to diquaternary ammonium salts have shown[1–4] that in these mass spectra intact dications are rarely observed, and then only in very low abundance. Dications are more frequently present in field desorption mass spectra[3,5,6] and their relative intensities are strongly dependent on the experimental conditions. In general, decomposition products of the dications dominate the spectra[7]. Dications of good intensity have so far only been observed in mass spectra obtained by electrohydrodynamic ionization[8]. In this method, solvated ions are extracted by high electric fields from liquids such as glycerol.

We report here the use of the new technique of thermospray (TSP) mass spectrometry[9,10] for the detection of intact dications from quaternary salts. In the TSP technique an electrolytic solution is sprayed into vacuum by passing the solution through a heated capillary, thus forming a jet of randomly charged droplets. Desolvation of ions is accomplished by heat transfer to the droplets. The TSP technique has been developed for on-line coupling of a mass spectrometer and a high-performance liquid chromatograph (HPLC). It is also possible to utilize a TSP/mass spectrometer system to obtain soft ionization spectra of unchromatographed samples that are thermally labile.

We have constructed a TSP system using a steel capillary of 80 μm i.d. One end of the capillary is heated to 250°C and connected to a jet chamber, which is maintained at 180°C, which, in turn, is linked via an orifice to a quadrupole mass analyzer (Finnigan 400, mass range 1–420). Aqueous solutions of the samples (2×10^{-4} mol L^{-1}) were introduced into the mass spectrometer via the heated capillary system. No further electrolyte was added.

The results of the TSP mass spectrometric studies of the diquaternary ammonium ions **1**–**6**[11] are displayed in Table 1. For all six compounds the $M^{2\oplus}$ dication forms the base peak of the mass spectrum. Additional information about the intact dication is provided by the $(M+1)^{\oplus}$ ion. Products arising from attachment of water to dications and other ions listed in Table 1 may also be present in the spectra; however, the intensities of these ions are generally weak (< 10%). Samples of 10 ng could readily be detected.

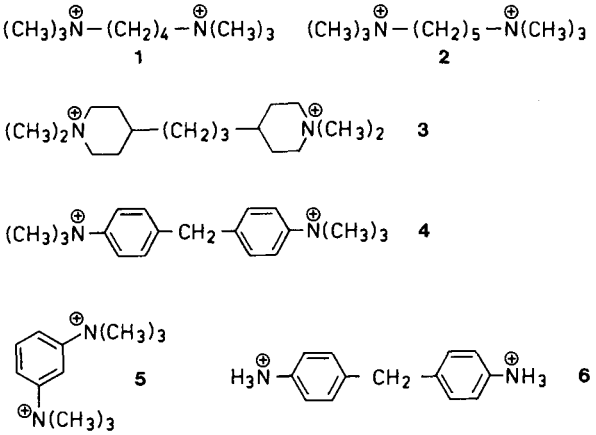

Table 1. Characteristic ions in the thermospray mass spectra of the diquaternary ammonium salts $\mathbf{1}2\mathbf{1}^{\ominus}$–$\mathbf{6}2\mathbf{1}^{\ominus}$ ($M^{2\oplus}2\mathbf{1}^{\ominus}$). $M^{2\oplus}$ is the base peak in all the spectra.

	Ions observed
1	$M^{2\oplus}$, $(M+1)^{\oplus}$ (m)
2	$M^{2\oplus}$, $(M+1)^{\oplus}$ (m)
3	$M^{2\oplus}$, $(M+1)^{\oplus}$ (w)
4	$M^{2\oplus}$, $(M-CH_3)^{\oplus}$ (m), $(M-2CH_3+H)^{\oplus}$ (w), $(M+1)^{\oplus}$ (w)
5	$M^{2\oplus}$, $(M-CH_3)^{\oplus}$ (m), $(M-2CH_3+H)^{\oplus}$ (m), $(M+1)^{\oplus}$ (w)
6	$M^{2\oplus}$, $(M-H)^{\oplus}$ (m), $(2M-3H)^{\oplus}$ (m)

m = intensity 10–50%, w = intensity < 10%.

Doubly charged ions have so far only been observed in TSP mass spectra of peptides of higher molecular weight[10]. The appearance of doubly charged ions has been taken as providing evidence for the participation of field effects in ion formation[10,12]. This assumption is supported by the close resemblance between the TSP spectra and the electrohydrodynamic ionization mass spectra[8] of the same diquaternary salts. However, it is surprising that in the electrohydrodynamic ionization spectrum of **5** the dication is absent. Thermospray mass spectrometry provides, so far without exception, abundant dications that are directly indicative of the molecular weight of diquaternary salts.

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[12] M. L. Vestal in A. Benninghoven: *Ion Formation from Organic Solids*, Springer, Heidelberg 1983.

Elementary Steps in Catalytic 1-Alkyne Coupling to Substituted Cyclooctatetraenes**

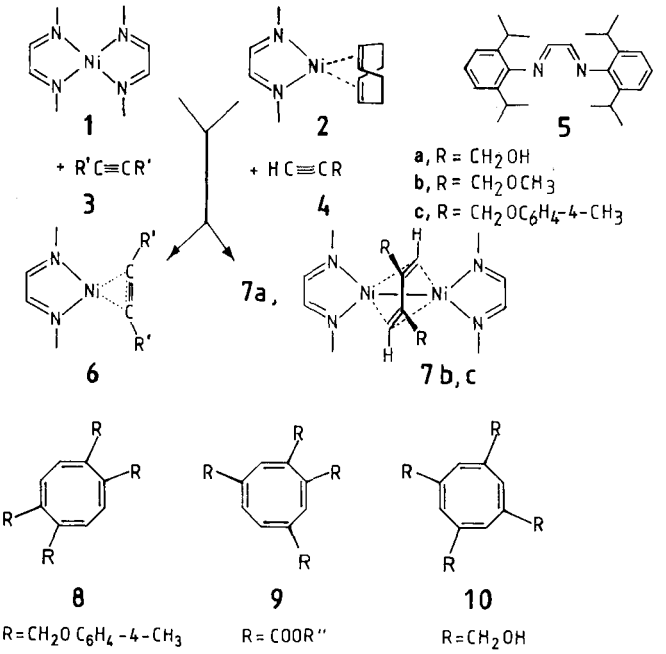
By *Rainer Diercks, Lutz Stamp, Jürgen Kopf*, and *Heindirk tom Dieck**

Nickel compounds have been well established as catalysts for the cyclotetramerization of acetylene to cyclooctatetraene (COT) ever since the publication of *Reppe*'s studies in this sector, but it was not until 1978 before a mechanism could be proposed that suitably describes the reaction of a COT-dinickel matrix and satisfactorily explains the competition between benzene formation and the thermodynamically unfavorable formation of an eight-membered ring[2].

The diazadiene(dad)-nickel(0) systems $(dad)_2Ni$ **1** and (dad)Ni(cod) **2** are the only precatalysts which exclusively cyclotetramerize alkynes[1,3]. The occurrence of new compounds in the reaction of **1** and **2** with the alkynes **3** and **4**, respectively, which are recognizable by a change in color from red-violet (**1**, **2**) to blue, prompted us to investigate the intermediates of the catalytic reaction. *N,N'*-ethanediylidenebis(2,6-diisopropylaniline) **5** served as diazadiene (dad).

Reaction of the disubstituted acetylenes **3** with **1** affords blue complexes **6** in which the alkyne and dad are coordinated to nickel[4] (UV/VIS: $\lambda_{max} \approx 620$ nm, IR: $\nu_{C\equiv C} = 1770-1820$ cm^{-1}). The reaction of **2** with 1-alkynes **4** leads to very similar blue intermediates **7** (UV/VIS: $\lambda_{max} \approx 640$ nm), which surprisingly show no vibration attributable to coordinated alkynes in the IR spectrum. Molecular mass determinations in benzene according to the method of *Beckmann* show that **7a** is present as a dimer. Hydrolysis of **7b** in an acid medium furnishes a product of mass $2M_{4b}+2$, which has been detected solely by mass spectroscopy.

In the 80-MHz ^{1}H-NMR spectrum of **6**, $R' = CH_2OCH_3$, the resonance of the OCH_2 protons appears as a sharp singlet at $\delta = 5.02$[11], whereas the resonance of the OCH_2 protons of **7b** appears as an AB system at $\delta = 3.10$, thus indicating diastereotopism of the H atoms. A lowering of symmetry can also be concluded from the ^{13}C-NMR spectrum, in which ten signals (from a maximum of twelve) are resolved for CH_3 and CH—C-atoms of the isopropyl groups.



7b was obtained from ethanolic solution in the form of bluish colored, almost cubic crystals which were suitable for an X-ray crystal structure analysis (Fig. 1).

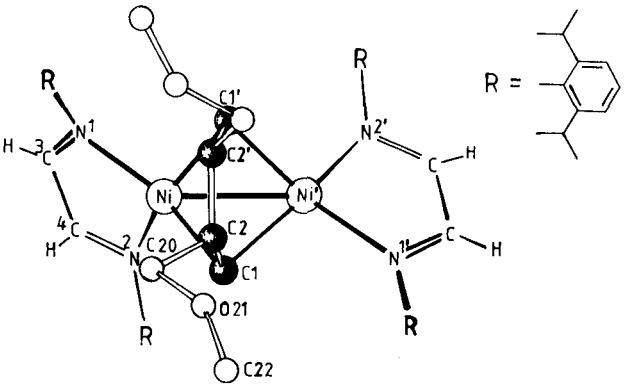


Fig. 1. Structure of **7b** in the crystal. $P4_12_12$, $a = 13.938(5)$, $c = 29.871(10)$ Å, $V = 5803.4$ Å^3, $Z = 4$, $R = 0.099$ for 2914 reflections with $I \geq 3\sigma(I)$; bond lengths Å; bond angles and torsion angles [°]; standard deviations (in brackets), given in units of the last decimal place: Ni-Ni' 2.541(2), Ni-N1 1.92(1), Ni-N2 1.95(1), Ni-C1 1.95(2), Ni-C2 2.43(2), Ni-C1' 2.00(2), Ni-C2' 2.41(2), C1-C2 1.29(3), C2-C2' 1.49(3), N1-C3 1.31(2), N2-C4 1.31(2), C3-C4 1.41(2), C2-C20 1.60(4), C20-O21 1.36(4), O21-C22 1.38(3); C1-Ni-C2 31.9(6), C2-Ni-C2' 35.9(7), C1-Ni-C1' 82.8(7), Ni-C1-Ni' 80.2(6), Ni-C1-C2 95.1(12), Ni-C1'-C2' 91.7(13), N1-Ni-N2 83.4(5), Ni-N1-C3 111.7(10), N1-C3-C4 117.1(14); N1-Ni-Ni'-N1' 79.5(6), N2-Ni-Ni'-N2' 156.3(10), C1-C2-C2'-C1' 7.4(27). Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD 50960, the names of the authors, and the journal citation.

According to the analysis, reaction of **2** and **4b** leads, presumably via an intermediate **6**, to formation of a binuclear nickel compound in which two alkyne molecules are coupled to a C_4 chain. This cisoid butadienediyl moiety lies C_2-symmetrically in a plane almost perpendicular to the Ni—Ni bond (2.54 Å); the planes of the two dad control ligands are rotated through ca. 90° to each other, so that a C_2 axis exists in the molecule, through the central C—C bond and the mid-point of the Ni—Ni bond. Also

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surprising is that the alkynes are coupled via the substituted centers.

The cyclotetramer **8** of the propargyl-*p*-tolyl ether **4c**, as sole low-molecular product of a catalyst reaction on **1**, has a highly symmetric 1,4,5,8-substitution pattern[3b]. The coupling of the alkynes in **7b** allows only this one substitution pattern for highly symmetric COT derivatives, not 1,3,5,7-substitution, and probably not 1,2,5,6-substitution.

The tetramerization of propargylates to **9**, R″ = Me, Et[1], could in principle, proceed via a structure **7**, since two substituents are adjacent in **9**. The major product **10** of the tetramerization of propargyl alcohol **4c**[3c] requires, by way of necessity, another alkyne coupling in the intermediate **7a**, which according to the NMR spectrum has a higher symmetry than **7b**; the structure of **7a**, is, however, still unknown.

The (dad)-nickel system thus apparently responds quite flexibly towards steric and/or electronic properties of the alkyne. The structure of **7b** clearly demonstrates that the reaction circumvents the formation of benzene derivatives, since a Diels-Alder reaction—as for example of a metallacyclopentadiene[5]—is no longer possible. The correlation in the unexpected stereochemistry between **7** and **8** and the finding that induction periods occur in catalyses with **1** and **2**—but not in reactions of **7** with 1-alkynes—suggest that **7** is indeed an intermediate of the catalytic sequence **4** → **6** → **7** → **8** and not a "parking lot" for 1-alkynes.

Experimental

7b: A solution of **4b** (100 mg, 1.43 mmol) in THF (10 mL) was added slowly in the absence of air to a solution of **2** (709.8 mg, 1.31 mmol) in 40 mL tetrahydrofuran (THF). After 24 hours' stirring at room temperature, all volatile components were removed from the deep-blue solution in vacuo at room temperature; the oily residue was dissolved in hot ethanol and filtered. Blue, cubic-shaped crystals of **7b** (490 mg, 74.2%) precipitated from the filtrate at room temperature. ^{1}H-NMR (CD_2Cl_2, TMS int.): $\delta = 0.52-1.22$ (more than 10 signals, CH_3), 2.55 (s, OCH_3), 2.71 (m, $CH(CH_3)_2$), 3.10 (dd, OCH_2), 3.83 (m, $CH(CH_3)_2$), 5.14 (s, "alkyne"-CH), 6.82—7.15 (H(aromat.)), 7.30 and 7.84 (N=C*H*).—^{13}C-NMR (CD_2Cl_2, TMS int.): $\delta = 22.4-28.4$ (10 signals resolved for CH, CH_3), 57.5 (OCH_3), 70.7 (OCH_2), 122.8—128.1 ($\approx$5 signals, CH), 128.3, 140.5, 141.8, 142.3, 151.9, 153.6 (at least 6 signals C quarternary).—UV/VIS (THF): $\lambda_{max} = 642$ nm.

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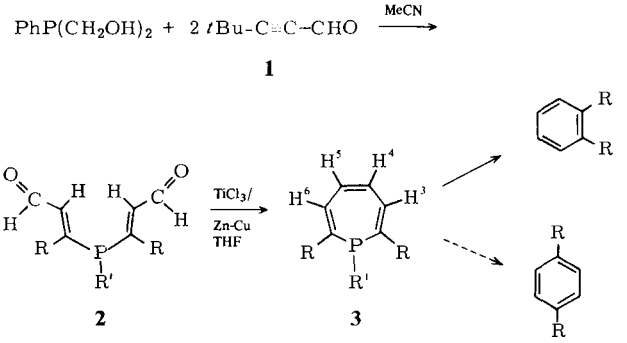
2,7-Di-*tert*-butyl-1-phenyl-1*H*-phosphepine—The First Stable, Monocyclic Phosphepine

By *Gottfried Märkl** and *Willibald Burger*

Of the 8π-heterocycles, oxepins and azepines are well-known stable compounds[1], whereas thiepins eliminate sulfur and readily decompose via bicyclic thianorcaradiene isomers to give benzene derivatives[2]. In contrast, 2,7-di-*tert*-butyl-substituted thiepins, which for steric reasons (eclipsed arrangement of the *tert*-butyl groups) cannot isomerize to the bicyclic isomers, are stable[3].

Monocyclic phosphepines were previously unknown. The 1-oxo-1-phenyl-λ^5-phosphepine[4] described by us previously decomposes in all attempts at its reduction—probably via the phosphanorcaradiene—with elimination of [PhP]; the recently prepared 3-phenyl-3-benzophosphepine[5] is also thermolabile and even at room temperature in solution is slowly converted into naphthalene.

With the synthesis of 2,7-di-*tert*-butyl-1-phenyl-1*H*-phosphepine **3a** we have now shown that for phosphepines substitution of the 2,7-positions by *tert*-butyl groups also prevents formation of the norcaradiene structure necessary for the decomposition.



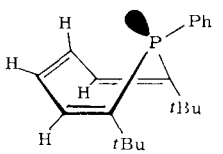
a, R′ = Ph, R = *t*Bu; **b**, R′ = Me, R = *t*Bu; **c**, R′ = R = Ph

Scheme 1.

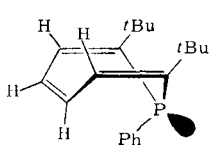
Phosphepine **3a** can be prepared as shown in Scheme 1. 4,4-Dimethyl-2-pentinal **1** is prepared from 3,3-dimethyl-1-butyne (*tert*-butylacetylene)[6] by reaction of the Mg-acetylide with ethyl orthoformate (yield 47%)[7]. The bis-adduct **2a** is obtained in 17—20% yield by Michael-like addition of bis(hydroxymethyl)phenylphosphane to **1** in acetonitrile (molar ratio 1 : 2, 16 h at room temperature, 2 h refluxing) via elimination of formaldehyde.

The key step in the synthesis of phosphepine **3a** is the reductive coupling **2a** → **3a** via a McMurry reaction[9, 10].

The $J_{H,H}$ coupling constants suggest[11] that **3a**, like all "epines" whose structure has been investigated analytically, is present in the boat form. Because of the stability of tertiary phosphanes to inversion it must be assumed that **3a** consists of a *syn/anti*-mixture of isomers.



anti-**3a**



syn-**3a**

3a is thermally stable. Whereas at 130 °C, 2,7-di-*tert*-butylthiepin undergoes sulfur extrusion to afford *o*-di-*tert*-butylbenzene[3], this is detected neither in the preparation of **3a** nor after its distillative purification. The *p*-di-*tert*-bu-

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tylbenzene isolated must therefore arise either from the reaction **2a** → **3a** or from **3a** under the conditions used for the McMurry reaction. This assumption is also suggested by the reaction of the dialdehydes **2b**, **c** with $TiCl_3$/Zn–Cu, where the phosphepines **3b**, **c** cannot be isolated.

2b undergoes a McMurry reaction to give *p*-di-*tert*-butylbenzene in 14% yield; under these conditions **2c** reacts to afford only traces of *p*-terphenyl, but *o*-terphenyl (m.p. 56 °C) is obtained in 15% yield. Formation of *o*-terphenyl is consistent only with decomposition of 1,2,7-triphenylphosphepine **3c**, which is not expected to be thermally stable.

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[8] **2a**; pale yellow crystals, m.p. = 121–121.5 °C (from *n*-hexane); ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 1.42 (d, ^4J(PH) = 1.13 Hz, *t*Bu), 5.73 (dd, ^3J(PH) = 5.30, ^3J(HH) = 7.70 Hz, =CH), 10.39 (dd, ^3J(HH) = 7.70, ^4J(PH) = 0.34 Hz, CHO), 7.37–7.57 (m, C_6H_5)); according to the results of NOE difference spectroscopy, **2a** has the (*E*,*E*)-configuration.—^{31}P-NMR ($CDCl_3$): δ = 4.28.—IR (KBr): ν(=CH) = 3060, 3080, ν(C–H in CHO) = 2760, 2890; ν(CO) = 1655, 1665 cm^{-1}.—*MS* (70 eV); *m/z* 330 ($M^{\oplus}$, 59%), 315 ($M^{\oplus}-CH_3$, 100), 301 ($M^{\oplus}$–CHO, 21), 287 ($M^{\oplus}-CH_3$–CO, 19), 219 ($M^{\oplus}$ – Me_3CC=CHCHO, 68).—UV (MeOH): λ_{max} = 241 nm (ε = 13700), 317 (5720), 371 (2020), 386 (1430).

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[10] **3a**: A solution of the dialdehyde **2a** (5 mmol) in tetrahydrofuran is added dropwise over 48 h to a suspension of $TiCl_3$ (50 mmol)/zinc-copper couple (100 mmol) [9] in refluxing tetrahydrofuran (THF) and the mixture refluxed for a further 3 h. After filtration, removal of solvent, and extraction with ether, a yellow oil is obtained. Chromatography on SiO_2 (petroleum ether/ether 4:1) and kugelrohr distillation at 90 °C/10^{-2} torr affords a colorless, crystalline product, m.p. = 78–80 °C, which surprisingly proved to be *p*-di-*tert*-butylbenzene (yield 4%); at 130–150 °C, **3a** distils as a pale yellow, viscous oil which can be purified by HPLC (Li Chromsorb, Si 100, Merck, particle size: 10 µ, column length: 25 cm, eluent: anhydrous *n*-hexane); yield 8–10%, colorless crystals, m.p. = 62–63 °C.—^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.40 (s, *t*Bu), 6.89 (AA'XX'Y system, calculated by Laocoon-Lame, ^3J(PH) = 10.0, ^3J(H3H4)(H5H6) = 6.50, ^4J(H3H5)(H4H6) = 0.05, ^5J(H3H6) = 1.28 Hz, ring-H3(H6)), 6.07 (^4J(PH) = 0.5, ^3J(H4H5) = 11.80 Hz, H4(H5)), 7.02 (s, C_6H_5), 7.05 (s, C_6H_5).—^{13}C-NMR (22.5 MHz, $CDCl_3$): δ = 31.46 (^3J(PC) = 9.98 Hz, C(CH_3)$_3$), 39.01 (^2J(PC) = 31.69 Hz, *C*(CH_3)$_3$), 152.08 (^1J(PC) = 21.13 Hz, C2(C7)), 131.13 (^2J(PC) = 6.46 Hz, C3(C6) [C4(C5)]), 129.71 (^3J(PC) = 15.26 Hz, C4(C5) [C3(C6)]), 138.34 (^2J(PC) = 16.0 Hz, C8), 129.69, 126.58 (3.52 Hz), 125.61 (C9, C10, C11).—^{31}P-NMR ($CDCl_3$): δ = –41.3.—UV (*n*-hexane): λ_{max} = 220 nm (ε = 44530); 255 (19950); 294 (7230).—IR (KBr); ν(C=H) = 3080, 3060, 3020 cm^{-1}; ν(C=C) = 1610, 1590.—MS (70 eV): *m/z* 298 ($M^{\oplus}$, 100%), 283 ($M^{\oplus}-CH_3$, 38), 255 ($M^{\oplus}-C_3H_7$, 77), 242 ($M^{\oplus}-C_4H_8$, 35), 241 ($M^{\oplus}-C_4H_9$, 41), 109 ($PhPH^{\oplus}$, 47), 108 ($PhP^{\oplus}$, 36). High resolution: $C_{20}H_{27}P$; *M*(calc.) = 298.18504; *M*(found) = 298.18436.

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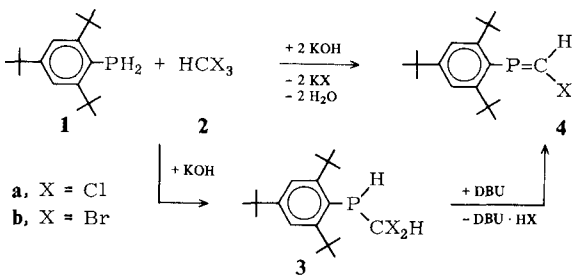
Easy Synthesis of Phosphaalkenes by a Phosphorus-Analogous Isocyanide Reaction and an Atypical Crystal Structure of a Tetracarbonyl(phosphaalkene)iron Complex**

By *Rolf Appel**, *Carl Casser*, *Michael Immenkeppel*, and *Falk Knoch*

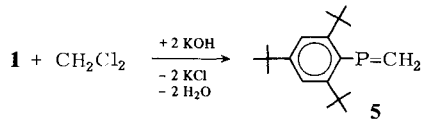
In recent years several reports have appeared on the synthetic possibilities offered by phosphaalkenes[1]. By analogy to the well-known isocyanide reaction, we have now discovered an additional easy synthesis of previously inaccessible phosphaalkenes substituted by hydrogen and halogen at the carbon.

The stable 2,4,6-tri-*tert*-butylphenylphosphane **1** reacts smoothly with trihalomethanes HCX_3 **2a**, **b** in the presence of potassium hydroxide to afford the phosphaalkenes **4a**, **b**. By observing the course of the reaction spectroscopically, the phosphanes **3a**, **b** formed from the dihalocarbene generated in situ and **1** can be unequivocally detected. Addition of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) converts **3a**, **b** quantitatively into **4a**, **b**.



In the crude product **4a**, **b** occur as a mixture of the *E*/*Z*-isomers from which one isomer could be isolated after chromatographic purification and recrystallization from acetonitrile/toluene (2:1). According to the spectroscopic results, **4b** is the isomer which we recently described and obtained only in low concentration using an alternative synthetic procedure[2]. We have therefore succeeded for the first time in isolating both isomers of a phosphaalkene in pure form. NMR data[3] and the results of elemental analysis and high resolution mass spectroscopy are in accord with the proposed structures. Attempts to prepare the phosphorus-analogous isocyanides by α-elimination of hydrogen halide from **4a**, **b** were unsuccessful until now.

In the analogously performed reaction of **1** with dichloromethane, methylene(2,4,6-tri-*tert*-butylphenyl)phosphane **5** is formed as colorless crystals. **5** was already obtained in 1982 by thermal elimination of chlorotrimethylsilane[4], but could only be detected by ^{31}P-NMR spectroscopy in the product mixture.



Phosphaalkenes can coordinate to transition-metal centers. The X-ray structure analysis of tetracarbonyl[2,4,6-tri-*tert*-butylphenyl(α-trimethylsilylbenzylidene)phosphane]-

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[**] Low-Coordinated Phosphorus Compounds, Part 34.—Part 33: [2].

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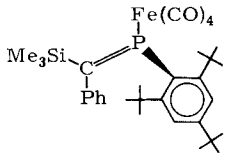
iron(0) **6**[2,5] reveals an unusual trigonal bipyramidal type structure with the η^1-bonded phosphaalkene ligand occupying an axial position. In view of its spatial requirements, this ligand should occupy an equatorial (bond angle 120°) rather than an axial position (bond angle 90°) as found for the recently described carbonyliron complex with a phosphaalkene ligand[6] and for a tetracarbonyliron compound with the very bulky diphosphene ligand[7].



6

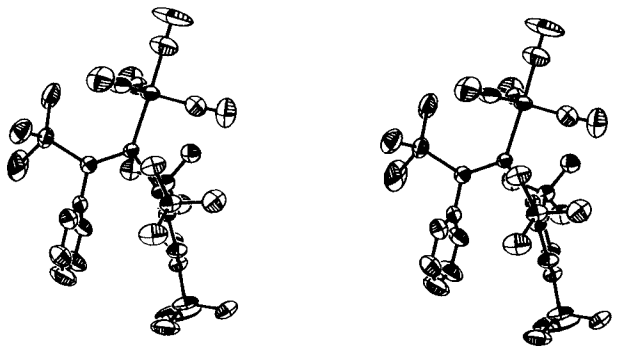


Fig. 1. Stereodiagram of the molecular structure of **6** [5].

Procedure

4a, b: Dry, powdered KOH (2.5 g) is added to a solution of **1** (2.78 g, 10 mmol) and **2a, b** (20 mmol) in 30 mL tetrahydrofuran. After completion of the exothermic reaction, the mixture is stirred for 24 h.

For the quantitative conversion (^{31}P-NMR monitoring), the solution is treated with 1–1.5 mL DBU. The solvent is removed and the residue taken up in 50 mL *n*-pentane. After the mixture has been filtered and the solvent removed in vacuo, the crude product is purified by column chromatography on silica gel (eluent, **4a**: *n*-hexane, **4b** ethyl acetate). The white solid thus obtained is recrystallized from acetonitrile/toluene (2:1). **4a**: m.p. = 108 °C. Yield **4a**: 1.02 g, **4b**: 0.5 g.

5: **1** (2.78 g, 10 mmol) is dissolved in 30 mL dichloromethane and dry, powdered KOH (2.5 g) added to this solution. After being stirred for 3 d at 25 °C, the solvent is removed in vacuo and the residue taken up in 50 mL *n*-pentane and separated from insoluble salts. The solvent is removed and the solid residue recrystallized from acetonitrile/toluene (2:1). M.p. 80 °C. Yield: 1.85 g.

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[3] Selected NMR parameters: ^{31}P-NMR (32.2 MHz, 85 H_3PO_4 ext.): **3a**: (C_6D_6) $\delta = -24.6$ (dd, J(PH) = 234.3, J(PCH) = 13.8 Hz); **3b**: (C_6D_6) $\delta = -16.9$ (dd, J(PH) = 240.6, J(PCH) = 15.2 Hz); **4a**: (C_6D_6) $\delta = 250.2$ (d, J(PCH) = 21.9 Hz); **4b**: ($CDCl_3$) $\delta = 262.4$ (d, J(PCH) = 23.9 Hz), **5**: (C_6D_6) $\delta = 288.6$.—^{1}H-NMR (90 MHz, TMS int.): **4a**: ($CDCl_3$) $\delta = 7.45$ (d, J(PCH) = 21.9 Hz, 1 H, P=CH); **4b**: ($CDCl_3$) $\delta = 1.32$ (s, 9 H, CH_3), 1.52 (s, 18 H, CH_3), 7.40 (d, J(PCH) = 23.9 Hz, 1 H, P=CH), 7.46 (s, broad, 2 H, Ph); **5**: (C_6D_6) $\delta = 1.32$ (s, 9 H, CH_3), 1.58 (s, 18 H, CH_3), 6.77 (dd, J(PCH) = 28.0, J(HCH) = 4.2 Hz, 1 H, P=CH), 7.05 (dd, J(PCH) = 32.8, J(HCH) = 4.2 Hz, 1 H, P=CH), 7.58 (s, broad, 2 H).—^{13}C{^{1}H}-NMR ($CDCl_3$, 20.0 MHz, TMS int.): **4a**: $\delta = 161.1$ (d, J(P=C) = 40.97 Hz); **4b**: $\delta = 31.3$ (s, pCH_3), 33.8 (d, J(PCCCC) = 7.3 Hz, oCH_3), 35.0 (s, $pCCH_3$), 38.1 (s, $oCCH_3$), 121.9 (d, J(PCCC) = 1.3 Hz, C-3-Ph), 137.3 (d, J(PC) = 56.6 Hz, C-1-Ph), 147.6 (d, J(P=C) = 49.7 Hz), 150.6 (s, C-4-Ph), 154.1 (d, J(PCC) = 2.3 Hz, C-2-Ph); **5**: $\delta = 31.5$ (s, pCH_3), 33.9 (d, J(PCCCC) = 7.4 Hz, oCH_3), 34.9 (s, $pCCH_3$), 38.2 (s, $oCCH_3$), 121.6 (d, J(PCCC) = 1.2 Hz, C-3-Ph), 141.2 (d, J(PC) = 58.9 Hz, C-1-Ph), 149.4 (s, C-4-Ph), 153.2 (d, J(PCC) = 1.8 Hz, C-2-Ph), 155.8 (d, J(P=C) = 38.9 Hz).
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[5] X-ray structure data for **6**: $P2_1$, $a = 1099.2(2)$, $b = 961.0(2)$, $c = 1613.7(3)$ pm, $\beta = 99.65(1)°$, $V = 1680.5(6) \times 10^6$ pm^3, $\rho_{calc} = 1.20$ g/cm^3, $Z = 2$; direct methods (SHELXTL), 4149 reflections, $R = 0.045$ ($R_w = 0.036$). Geometry: within the limits of the precision of the measurements, the P atom is planar coordinated. Angles [°]: PFeC(ax) = 177.6(2), FeP=C 126.5(2), PFeC(eq) 88–92. Bond lengths [pm]: PFe 226.3(1), P=C 167.0(4). Further details on the crystal structure analysis can be obtained from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, by quoting the depository number CSD 51027, the names of the authors, and the journal citation.
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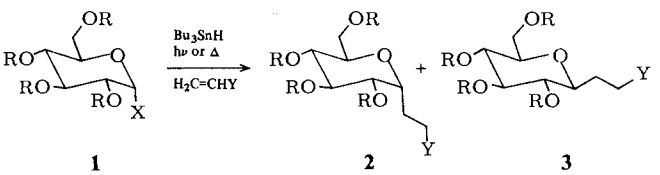
Conformation of Glycosyl Radicals: Radical Stabilization by β-CO Bonds**

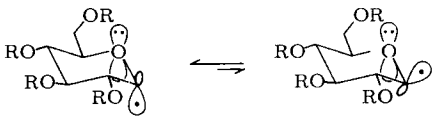
By *Jacques Dupuis, Bernd Giese*, Daniel Rüegge, Hanns Fischer, Hans-Gert Korth,* and *Reiner Sustmann*

Reaction of tetraacetylglucosyl bromide **1a** (X = Br) with nBu$_3$SnH in the presence of acrylonitrile or methyl acrylate affords the CC coupling product **2** with axial arrangement of the substituents on C-1[1]. This stereoselectivity was evidenced by the occurrence of the σ-radical **4**[1,2], which, because of interaction with the non-bonding electron pair on the ring oxygen atom, should be more stable[2] and more nucleophilic[3] than the σ-radical **5**. However, the high stereoselectivity of this reaction decreases from over 50 (**2a** : **3a** = >98 : <2) to 3.5 (**2b** : **3b** = 78 : 22) if the tetramethylglucosyl bromide **1b** (X = Br) is employed instead of **1a** (X = Br). This finding prompted us to measure the ESR spectra of the intermediate glucosyl radicals.



1 **2** **3**

a, R = Ac; **b**, R = CH_3; X = Cl, Br; Y = CN, CO_2CH_3



4 **5**

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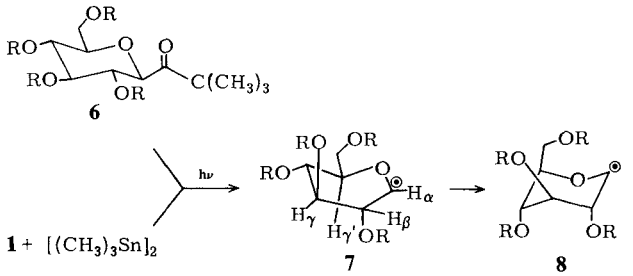
Photolysis of the ketones **6**[4] or abstraction of bromine from **1a** (X = Br) with trimethyltin radicals led to radicals whose ESR spectra are reconcilable with a boat conformation, as in the radical **7** in which the substituents on C-2 and C-3 are axial. Supporting evidence for this structure is provided by a) the small β-coupling constant, which points to an equatorial arrangement of the β-CH bond[5], b) the occurrence of a relatively large γ-coupling, caused by a W-arrangement of the electrons and, hence, an extensively equatorial γ-CH bond, and c) the unusually large α-coupling constants for radicals of the type RĊHOR′, indicating an almost planar radical[6] (Table 1).



a, R = Ac; **b**, R = CH_3

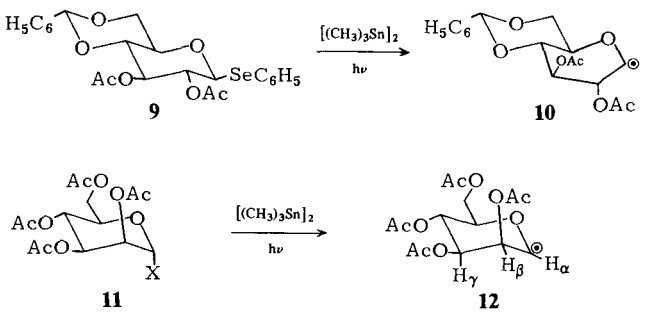
Table 1. ESR data of the glucosyl and mannosyl radicals **7**, **10**, and **12**.

Radical	T [°C]	Coupling constants [G] α-CH	β-CH	γ′-CH	γ-CH	g-Factor
7a [a]	−27	18.44	11.79	3.77	1.73	2.0031
	40	18.20	12.91	3.56	1.46	
7a [b]	−30	18.00	13.64	3.48	1.45	2.0031
	20	17.96	14.07	3.45	1.41	
7b [c]	−22	17.99	10.58	3.88	2.21	2.0032
	44	17.92	12.74	3.59	1.84	
10 [d]	−24	18.02	10.02	3.84	1.64	2.0033
	33	18.02	11.99	3.76	1.42	
12 [e]	20	18.52	3.53	3.07	—	2.0031
	95	18.34	4.24	3.07	—	

[a] Photolysis of **6a** in 2-propanol. [b] Photolysis of $[(CH_3)_3Sn]_2$ in the presence of **1a** (X = Br) in tetrahydrofuran. [c] Photolysis of **6b** in 2-propanol. [d] Photolysis of $[(CH_3)_3Sn]_2$ in the presence of **9** in toluene. [e] Photolysis of $[(CH_3)_3Sn]_2$ in the presence of **11** in tetrahydrofuran.

The transformation of the $^4C_1$ conformation of the educts **1** and **6** into the $B_{2,5}$ conformation[7] of the radical **7** involves an interconversion of the substituents on C-2 and C-3 from the equatorial into the axial position. The ESR spectra leave it open as to whether the $^1C_4$ conformation **8**, in which all substituents are axial, is also realized by inverting the ring at C-5. In order to differentiate between these two possibilities, the corresponding bicyclic glucosyl radical was generated from the bicyclic selenoglucoside **9**[8]. The α-, β-, and γ-coupling constants (Table 1) of the radicals generated from **1**, **6**, and **9** are to a great extent consistent in magnitude and temperature dependence. In the case of the bicyclic glucosyl radical, this is reconcilable only with the boat conformation **10**, since the *trans*-coupling of the two rings makes an inversion into the $^1C_4$ chair conformation impossible. The similarity of the ESR signals of the radicals generated from **1**, **6**, and **9** suggests that the monocyclic glucosyl radicals are also present in the boat conformation **7**.

In contrast, in the mannosyl radical **12** the $^4C_1$ conformation of the educt **11** is preserved. This is evidenced by a) the small β-coupling constant of about 4 G, which is reconcilable only with an equatorial arrangement of the β-CH bond and b) the disappearance of the resulting γ-coupling over two CC bonds (Table 1).



Accordingly, the glycosyl radicals generated from the glucose derivatives **1**, **6** and **9** and the mannose derivative **11** have a largely coplanar arrangement of the β-CO bond and the half-occupied orbital. *Gilbert* and *Norman* et al. have observed an analogously preferred conformation in open-chain radicals of the type RŌCHCHR′OR″[6], which can be explained in terms of an interaction between the half-occupied orbital at the radical center and σ* orbital of the C–OR bond. The SOMO/LUMO interaction is especially pronounced in the glycosyl radicals, since the SOMO energy of the radicals is enhanced by the neighboring oxygen atom. In the glucosyl radicals it can apparently overcompensate the repulsive interactions in the transition from the chair to the boat conformation.

The radical-stabilizing effect of the axial β-CO bond is also noticeable in the rates of abstraction of halogen from glycosyl chlorides. Thus, kinetic measurements of competition reactions in benzene at 80 °C show that tributyltin radicals abstract the halogen atom of the mannosyl chloride **11** (X = Cl) 7.8 times more rapidly than the halogen atom of the glucosyl chloride **1a** (X = Cl). Only in the reaction of the mannose derivative is the β-CO bond axial in the transition state of the radical formation; in the glucose derivative the stabilizing effect of the β-CO bond can only be effective after change of conformation. Thus, this stereoelectronic effect also has an influence on the rate of formation of the radicals[9].

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[1] a) B. Giese, J. Dupuis, *Angew. Chem. 95* (1983) 633; *Angew. Chem. Int. Ed. Engl. 22* (1983) 622; b) R. Adlington, J. E. Baldwin, A. Basak, R. P. Kozyrod, *J. Chem. Soc. Chem. Commun. 1983*, 944.

[2] B. Giese, J. Dupuis, *Tetrahedron Lett. 25* (1984) 1349; see also: F. Baumberger, A. Vasella, *Helv. Chim. Acta 66* (1983) 2210; J. P. Praly, *Tetrahedron Lett. 24* (1983) 3075.

[3] B. Giese, J. Dupuis, T. Hasskerl, J. Meixner, *Tetrahedron Lett. 24* (1983) 703.

[4] The ketones **6a** and **6b** were synthesized from the D-glycero-D-guloheptoic acid by acetylation or methylation, respectively, conversion into the acid chloride, and reaction with *tert*-butylmagnesium bromide. The ^{1}H-NMR coupling constants of the ring protons were all 9.40 Hz in **6a** and 9.20 Hz in **6b**. For photolysis conditions see: L. Wymann, T. Kaiser, H. Paul, H. Fischer, *Helv. Chim. Acta 64* (1981) 1739.

[5] The coupling constants of the equatorial and axial H-atoms in carbohydrate radicals were previously determined as 12 and 30 G, respectively: B. C. Gilbert, D. M. King, C. B. Thomas, *J. Chem. Soc. Perkin Trans. 2 1981*, 1186; *ibid. 1983*, 675.

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[7] The cationic transition from the chair to the boat conformation has been previously discussed: R. U. Lemieux, K. B. Hendriks, R. V. Stick, K. James, *J. Am. Chem. Soc. 97* (1975) 4056.

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[8] **9** was synthesized from phenyl-1-seleno-β-D-glucoside by transacetalization with benzaldehyde dimethyl acetal and subsequent acetylation. The ^{1}H-NMR coupling constants of the protons on the pyran ring of **9** are $J_{1,2}=10.10$, $J_{2,3}$ 8.50, and $J_{3,4}=J_{4,5}=9.35$ Hz.

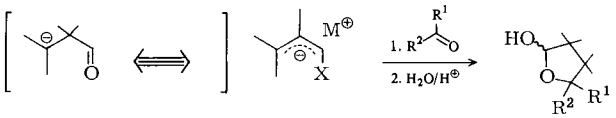
[9] For the significance of analogous radical-stabilizing effects see: P. S. Skell, K. J. Shea in J. Kochi: *Free Radicals, Vol. 2*, Wiley, New York 1973; D. H. R. Barton, W. Hartwig, W. B. Motherwell, *J. Chem. Soc. Chem. Commun. 1982*, 447.

Highly Enantioselective Homoaldol Additions with Chiral *N*-Allylureas—Application to the Synthesis of Optically Pure γ-Lactones**

By *Hanno Roder, Günter Helmchen*, Eva-Maria Peters, Karl Peters,* and *Hans-Georg von Schnering*

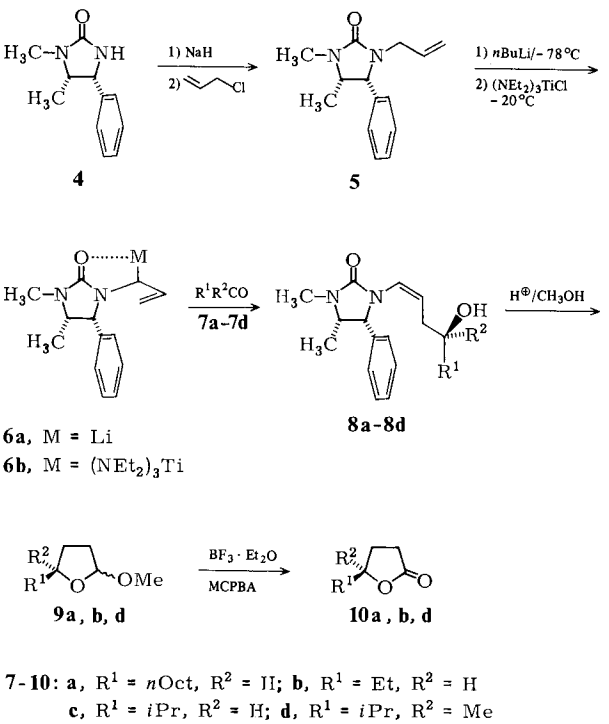
Dedicated to Professor Ulrich Schmidt on the occasion of his 60th birthday

In favorable cases, the reaction of aldehydes and ketones with hetero-substituted allylmetal compounds **2** proceeds with high regio- and diastereoselectivity (X = OCON*i*Pr$_2$[1a], X = NR–CO–NR$'_2$[1b]). Since the products can be hydrolyzed to aldehydes, which react to lactols **3**, compounds **2** function as synthetic equivalents of homoenolates **1**. Oxidation of the lactols affords lactones, many of which are important pheromones, terpenes, or chiral synthetic building blocks which are accessible via the "homoaldol reaction" in only one CC coupling step.



1 **2** **3**

We have now developed the first enantioselective homoaldol reaction involving a chiral allyl system of type **2**[2,3]. For this purpose we use as a novel reagent for asymmetric synthesis the cyclic urea derivative **4**, accessible in one step by fusing (−)-ephedrinium chloride with urea[4] [55–65%, m.p. = 177–179 °C, $[\alpha]_D^{25}$ −44.5 (*c* = 3, methanol)]. Using standard methods, one obtains from **4** the *N*-allyl derivative **5** [92%, m.p. = 68–69.5 °C, $[\alpha]_D^{22}$ +22.7 (*c* = 3, methanol)]. **5** can be smoothly deprotonated with *n*-butyllithium to the allyllithium compound **6a** and transmetalated[1a] to **6b** (−20 °C, red-orange solution) with chlorotris(diethylamino)titanium[5]. Reaction of the titanium compound **6b** with the aldehydes **7a–c** as well as, surprisingly, *with the methyl ketone* **7d** leads highly stereoselectively to the homoaldol adducts **8a–d**. These adducts have, as expected, a *cis*-configurated double bond[1,6] and can be obtained diastereomerically pure by recrystallization[7] (Table 1). The pure enamides **8a**, **b**, **d** are methanolyzed analogously to that described in [1b] to the *O*-methyllactols **9a**, **b**, **d**; the reagent **4** can be re-isolated in 95–98% yield by extraction. The crude compounds **9** can be directly oxidized with *m*-chloroperbenzoic acid (MCPBA) to the γ-lactones **10a**, **b**, **d** (Table 2) using the method described by *Grieco* et al.[8]. The configuration of **10a** and **10b**, whose enantiomers are the pheromones of various species of beetles[9], as well as that of **10d** were determined by comparison of the optical rotations with reliable literature data (Table 2). The configuration of the reagent **4** is



7-10: **a**, R^1 = *n*Oct, R^2 = H; **b**, R^1 = Et, R^2 = H
c, R^1 = *i*Pr, R^2 = H; **d**, R^1 = *i*Pr, R^2 = Me

Table 1. Reaction of the allyltitanium compound **6b** with the carbonyl compounds R^{1}R^{2}CO, **7a–d**, to give the homoaldol adducts **8a–d** (THF, −20 °C).

Homoaldol adduct [a]	Yield [%] [b]	Diastereosel. [c]	Yield [%] [d]	Diastereomeric ratio [d]
8a	96	94 : 6	61	≥200 : 1
8b	94	96 : 4	63	>200 : 1
8c	95	96 : 4	—	
8d	93	98 : 2	81	150 : 1

[a] Predominant homoaldol adduct. All compounds were characterized by CHN analyses (±0.3%) as well as by ^{1}H-NMR (400 MHz) and mass spectra. [b] Relative to **5**. [c] Diastereoselectivity was determined for **8a**, **b** by HPLC and for **8a**, **c**, **d** by ^{1}H-NMR (400 MHz). [d] After recrystallization from *n*-hexane or *n*-hexane/ethyl acetate.

Table 2. Methanolysis of the homoaldol adducts **8a**, **b**, **d** to the *O*-methyllactols **9a**, **b**, **d** and their Grieco oxidation [8] to the optically active γ-lactones **10a**, **b**, **d**.

γ-Lactone [a]	Yield [%] [b]	$[\alpha]_D$	Absol. config.
10a	99	$[\alpha]_D^{20}$ −41.1 [c] (*c* = 5, CH_3OH)	*S*
10b	79	$[\alpha]_D^{22.5}$ −53.7 [d] (*c* = 1, CH_3OH)	*S*
10d	97	$[\alpha]_D^{23}$ −10.5 (*c* = 3, CH_3OH) $[\alpha]_D^{20}$ −10.9 [e] (*c* = 1, $CHCl_3$)	*R* [e]

[a] Purified by liquid chromatography and kugelrohr distilled. [b] Yield relative to the diastereomerically pure homoaldol adducts **8a**, **b**, **d**. [c] Rotation of natural (*R*)-**10a**: $[\alpha]_D^{20}$ +41.1 (*c* = 5, CH_3OH); G. T. Muys, B. van der Ven, A. P. Dejonge, *Appl. Microbiol. 11* (1963) 389. [d] Rotation of (*R*)-**10b** prepared from L-glutamic acid: $[\alpha]_D^{20}$ +53.2 (*c* = 1, CH_3OH); for (*S*)-**10b**: $[\alpha]_D^{20}$ −53.2 (*c* = 1, CH_3OH); U. Ravid, R. M. Silverstein, L. R. Smith, *Tetrahedron 34* (1978) 1449. [e] The absolute configuration was determined by crystal structure analysis of **8c** (Fig. 1). Rotation of (*R*)-**10d** prepared from (*R*)-linalool (92.4% *ee*): $[\alpha]_D^{21}$ −10.2 (*c* = 1.07, $CHCl_3$); K. Mori, T. Ebata, S. Takechi, *Tetrahedron 40* (1984) 1761.

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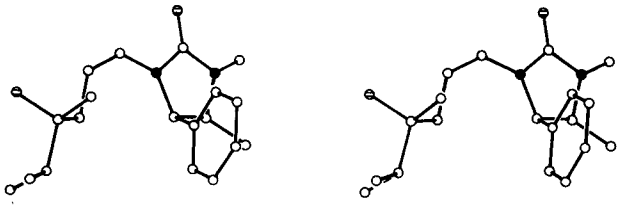
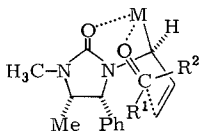
established by a crystal structure analysis of the enamide **8d** (Fig. 1).



„Fig. 1. Stereoscopic projection of the structure of **8d** in the crystal. Further details of the crystal structure investigation can be obtained from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, by quoting the depository number CSD 50966, the names of the authors and the journal citation.

For rationalization of configurative correlational relationships of the homoaldol addition, we assume that the reaction proceeds via a chair-like transition state in which the larger substituent at the carbonyl group preferentially adopts the equatorial position[10].



11, M = $Ti(NEt_2)_3$

The homoaldol additions described do not depend on the concentration of the reactants and, because of the ready accessibility and re-isolability of the reagent **4**, can be performed on a large scale. Both enantiomers of **4** are available. Because of the high stereoselectivity of the reaction and the possibility of subsequent purification by crystallization, the products can be obtained enantiomerically pure.

General Procedure

8: *n*-Butyllithium (0.11 mol, ca. 2 M in hexane) is added to 30 mL tetrahydrofuran (THF) (under an inert gas atmosphere at −78 °C) and the mixture stirred. A solution of **5** (0.1 mol) in 75 mL THF is added dropwise to this mixture, and after 25 min a solution of chlorotris(diethylamino)titanium (0.11 mol) in 30 mL THF is also added dropwise. The mixture is warmed up to −20 °C and 45 min later a solution of **7** (0.10 mol) in 10 mL THF is injected in. After ca. 2 h, water is added and the mixture is taken up in ether and extracted with 10% $NaHSO_3$ and with water. The enamides **8** obtained from the ether solution after drying and concentrating are chemically largely pure (see Table 1).

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4, 92841-65-1; **5**, 92720-98-4; **6a**, 92720-96-2; **6b**, 92720-97-3; **7a**, 124-19-6; **7b**, 123-38-6; **7c**, 78-84-2; **7d**, 563-80-4; **8a**, 92720-99-5; **8b**, 92721-00-1; **8c**, 92721-01-2; **8d**, 92721-02-3; **9a**, 92721-03-4; **9b**, 74577-87-0; **9d**, 92721-04-5; **10a**, 69830-92-8; **10b**, 41035-07-8; **10d**, 92721-05-6; CH_2=$CHCH_2Cl$, 107-05-1; $(Et_2N)_3TiCl$, 6607-37-0.

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[2] The alkylation of some chiral reagents of the type **2** has already been studied: a) H. Ahlbrecht, G. Bonnet, D. Enders, G. Zimmermann, *Tetrahedron Lett. 21* (1980) 3175; b) T. Mukaiyama, H. Hayashi, T. Miwa, K. Narasaka, *Chem. Lett. 1982*, 1637.

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[4] This reaction has already been performed with (±)-ephedrine, but on the basis of mechanistic considerations, the product was incorrectly assigned the *trans*-configuration: W. J. Close, *J. Org. Chem. 15* (1950) 1131.

[5] M. T. Reetz, R. Urz, T. Schuster, *Synthesis 1983*, 540.

[6] a) H. Ahlbrecht, *Chimia 31* (1977) 391; b) A. N. Tischler, M. H. Tischler, *Tetrahedron Lett. 1978*, 3407.

[7] An allylmagnesium compound prepared from **6a** by transmetalation with $MgBr_2 \cdot Et_2O$ exhibits high γ-regioselectivity but no stereoselectivity.

[8] P. A. Grieco, T. Oguri, Y. Yokohama, *Tetrahedron Lett. 1978*, 419.

[9] a) J. W. Wheeler, G. M. Happ, J. Araujo, J. M. Pasteels, *Tetrahedron Lett. 1972*, 4635; b) R. M. Silverstein, J. C. Young, *ACS Symp. Ser. 23* (1976) 1.

[10] The change in the notation for the absolute configuration in the series **8a**—**d** and **10a**, **b**, **d** (cf. Table 2) is determined by the alteration in the substituent priorities.

A Binuclear, Mixed-Valence $Mo^{VI/V}$-Complex; The Crystal Structure of $[(C_9H_{21}N_3)_2Mo_2^{VI}O_5](Br_3)_2$

By *Karl Wieghardt**, *Gabriele Backes-Dahmann*, *Willy Herrmann*, and *Johannes Weiss*

Binuclear, oxo-bridged complexes of molybdenum(VI-IV) have been discussed as active centers in the enzymes nitrate-reductase, sulfite-oxidase, and xanthine-oxidase[1]. ESR spectra of the active forms of these enzymes indicate an O,N,S-coordinated Mo^V center, thus suggesting that mixed-valence complexes of the type Mo^V/Mo^{IV} or Mo^{VI}/Mo^V could be present. For the former type there is only one well characterized example[2]; we report here on the characterization of the first mixed-valence Mo^{VI}/Mo^V complex.

Oxidation of $LMo(CO)_3$[3] with semiconcentrated nitric acid furnishes the yellow, diamagnetic cation $[L_2Mo_2^{VI}O_5]^{2\oplus}$ **1**, where L is the facially coordinated *N,N',N''*-trimethyl-1,4,7-triazacyclononane ligand. Salts of **1** with $(Br_3)^{\ominus}$, $PF_6^{\ominus}$ and $ClO_4^{\ominus}$ have been isolated in the crystalline state[4].

According to the X-ray structure analysis of **1** $(Br_3)_2$[5] a binuclear, μ_2-oxo-bridged cation with two pseudooctahedrally coordinated molybdenum(VI) centers is present (Fig.

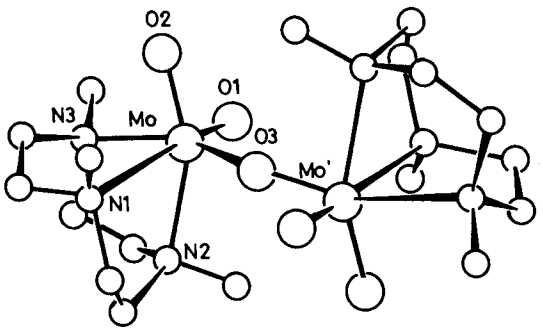

Fig. 1. Structure of **1** in the crystal of **1** $(Br_3)_2$; selected bond lengths [Å] and angles [°]. Mo-O1 1.694(7), Mo-O2 1.696(7), Mo-O3 1.898(1), Mo-N1 2.325(8), Mo-N2 2.355(8), Mo-N3 2.290(9); O1-Mo-O2 104.7(4), O2-Mo-O3 103.6(2), O1-Mo-O3 104.4(3), N1-Mo-O3 90.0(2), N1-Mo-N2 73.2(3), N2-Mo-N3 74.2(3), N1-Mo-N3 74.3(3), Mo-O3-Mo' 180.0.

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1). Each Mo^{VI} ion is surrounded by two terminal oxo groups, a bridging oxygen atom and three N atoms of the cyclic amine. The cation has C_i symmetry; the Mo–O–Mo-group is linear. The structural details of the $Mo_2O_5^{2\oplus}$ moiety compare well with those of other analogous complexes[6].

The chemical reduction of **1** with $Na[BH_4]$ or N_2H_4 in H_2O or acetonitrile leads to deep-blue, paramagnetic solutions of $[L_2Mo_2O_5]^{\oplus}$ **2**; this reduction can also be carried out electrochemically. The electron excitation spectrum of **2** shows intervalence bands at 753 ($\varepsilon = 2.6 \times 10^3$ L mol^{-1} cm^{-1}) and 909 nm (2.7×10^3). An effective magnetic moment of 1.7 μ_B was determined for **2** in solution at 25 °C by NMR spectroscopy using the method of *Evans*. The cyclovoltammogram of $\mathbf{1}(PF_6)_2$ in acetonitrile (Fig. 2) shows two electrochemically and chemically reversible electron transfers between +1.8 and −1.7 V (vs. Ag/AgCl) at redox potentials of −0.77 and −1.88 V referred to the internal redox system ferrocenium/ferrocene[7]. The following redox scheme can therefore be formulated.

$$[L_2Mo_2O_5]^{2\oplus} \underset{-e^-}{\overset{+e^-}{\rightleftharpoons}} [L_2Mo_2O_5]^{\oplus} \underset{-e^-}{\overset{+e^-}{\rightleftharpoons}} [L_2Mo_2O_5]$$

1 **2** **3**

3 is a binuclear Mo_2^V species.

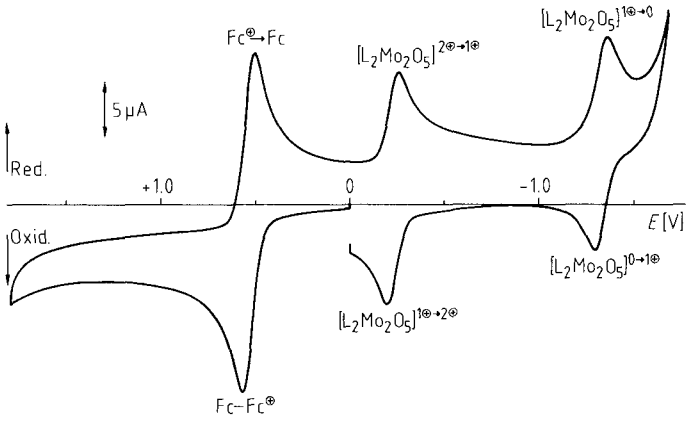

Fig. 2. Cyclovoltammogram of $\mathbf{1}(PF_6)_2$ (0.56×10^{-3} mol L^{-1}) in acetonitrile (supporting electrolyte: 0.1 mol L^{-1} ($NnBu_4$)PF_6; internal standard: 0.7×10^{-3} mol L^{-1} ferrocene (Fc); scan rate 0.1 V/s; platinum electrode: 7.1 mm^2 surface area; vs. Ag/AgCl).

A measure of the stability of the mixed valence Mo^{VI}/Mo^V binuclear complex is the comproportionation constant K_c, which, calculated from the two redox potentials, is 6×10^{18}.

$$Mo_2^{VI} + Mo_2^V \overset{K_c}{\rightleftharpoons} 2[Mo^{VI}Mo^V]$$

1 **3** **2**

Such a large value would indicate a complete delocalization of the unpaired electron in **2**[8].

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[4] *Procedure:* A suspension of 0.36 g $LMo(CO)_3$ [3] (L = *N,N,N''*-trimethyl-1,4,7-triazacyclononane) in 15 mL semiconcentrated nitric acid was stirred for 6 h at 22 °C. The resulting clear, orange solution was treated carefully with 5 mL of a saturated NaBr solution (evolution of Br_2), whereupon **1** $(Br_3)_2$ separated out as a yellow solid. This was filtered off, rapidly washed with cold ethanol and ether, and dried (yield 0.12 g). The compound can be recrystallized from water or acetonitrile, and precipitated as $\mathbf{1}(PF_6)_2$ or $\mathbf{1}(ClO_4)_2$ by addition of $NaPF_6$ or $NaClO_4$, respectively.—All salts free of water of crystallization gave correct elemental analyses.—IR (KBr [cm^{-1}]): ν(Mo=O): 930 vs, 905 vs; ν(as)(Mo–O–Mo): 770 vs. Solutions of $\mathbf{1}(PF_6)_2$ in H_2O or CH_3CN can be reduced in an argon atmosphere with N_2H_4 or $Na[BH_4]$ to the blue Mo^V/Mo^{VI} mixed-valence species **2**. Electrochemical reduction gives the same product. Oxidation with O_2 leads to reformation of yellow **1**. Attempts to isolate **2** as a salt failed.

[5] X-Ray structure analysis: $\mathbf{1}(Br_3)_2$: $P2_1/n$, $a = 8.959(2)$, $b = 11.076(2)$, $c = 17.208(2)$ Å, $\beta = 91.56(1)°$ at 22 °C, $V = 1707$ Å^3, $Z = 2$; 1652 independent reflections ($I \geq 2.5\sigma(I)$); Syntex $P2_1$, $Mo_{K\alpha}$, $\lambda = 0.71069$ Å, ϑ-2ϑ-scan ($3° \leq 2\vartheta \leq 60°$C); empirical absorption correction ($\mu = 77.1$ cm^{-1}); solution by Patterson and Fourier syntheses; $R = 0.049$, $R_w = 0.040$, atoms other than H anisotropic, H atoms (calculated) constantly isotropic (SHELXTL). Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD 50967, the names of the authors, and the journal citation.

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[7] Electrochemistry: In each case the two peak potential differences (ΔE_p) are ca. 65 mV; the peak current functions for both electron transfers are independent of the variation in voltage and are almost equal in magnitude.—The coulometric reduction of $\mathbf{1}(PF_6)_2$ at a mercury-pool electrode at −0.9 V (vs. Ag/AgCl) yields 1.02 ± 0.02 electrons per dimeric cation. During the electrolysis the color of the sample solution changes from bright yellow to deep blue. The coulometric reduction could not be accomplished at −1.7 V (vs. Ag/AgCl) since the product of reduction is not stable on such a time scale (ca. 30 min). However, here also, the diagnostic criteria clearly point to a one-electron transfer.

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[3+2]-Cycloaddition Reactions of a Stable Phosphaalkyne—Transition from Singly to Doubly Coordinated Phosphorus**

By *Wolfgang Rösch* and *Manfred Regitz**

The potential of phosphaalkynes to undergo cycloadditions has largely been untapped[1]. Accordingly, we have studied the cycloadditions of the only phosphaalkyne which is stable at room temperature, 2,2-dimethylpropylidynephosphane ("1-phospha-2-*tert*-butylacetylene"), **1**, with 1,3-dipoles of the diazoalkane, azide, nitrile oxide, and nitrilimine type. Reactions involving conversion of singly into doubly coordinated phosphorus open up access to a multitude of novel, aromatic, five-membered phosphorus heterocycles.

The diazomethane derivatives **2a**—**f** react with **1** in ether at 20 °C to afford the 1*H*-1,2,4-diazaphospholes **4a**—**f**. Only in the case of **2e** did it prove possible to isolate the initially formed 3*H*-1,3,4-diazaphosphole **3e** [^{1}H-NMR ($CDCl_3$): $\delta = 3.50$ (d, 1 H, $^2J_{P,H} = 8.1$ Hz, H-3)], which isomerizes to **4e** in solution. All compounds exhibit NH absorptions in the IR (KBr, $\nu = 3100$—3180) and ^{1}H-NMR spectra ($CDCl_3$, $\delta = 11.8$—13.1).

Both cycloadditions of diazomethane derivatives to chloro(2-trimethylsilylbenzylidene)phosphane ("1-chloro-

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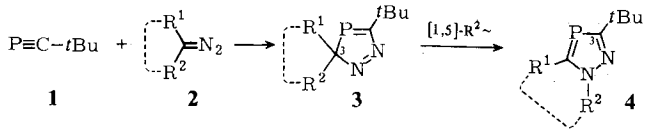


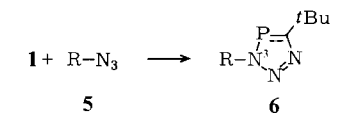
	a	b	c	d	e	f	g	h
R^1	H	Me	*t*Bu	COPh	CO_2Me	$POPh_2$		
R^2	H	H	H	H	H	H		

2-phenyl-2-trimethylsilyl-1-phosphaethene"), which involve elimination of chlorotrimethylsilane, and condensations of 1,3-bis(dimethylamino)-2-phosphaallyl chlorides with hydrazine derivatives[4] lead via independent routes to the same series of heterocycles. In the case of α-diazocarbonyl compounds such as **2g, h**, formation of **3g, h** is rapidly followed by sigmatropic [1,5]-shift of the acyl group to give the annelated diazaphospholes **4g, h**[5].

Diazaphospholes are distinguished by their ^{31}P- and ^{13}C-NMR signals (for C-3 and C-5) (Table 1). The magnitude of the phosphorus coupling with C-5 rules out an inverted dipole orientation as do the P couplings with the 5-substituents [e.g. ^1H-NMR ($CDCl_3$): **4a**: $\delta = 8.22$ (d, 1H), $^2J_{P,H} = 43.6$ Hz, H-5); **4b**: $\delta = 2.55$ (d, 3H, $^3J_{P,H} = 9.3$ Hz, 5-Me)].

The azide dipoles **5a—c, e**, even the hydrazoic acid **5a**, add smoothly to **1** in ether at 20°C to give the 3*H*-1,2,3,4-triazaphospholes **6**; the ^{31}P-NMR signals are accordingly strongly shifted to low field (Table 1).

From the phosphorus coupling constants with the original azide moieties in **6a—c**, the same regiochemistry as that of the diazoalkane dipoles can be derived and allows a subsequent substituent shift to be excluded [e.g. ^1H-NMR ($CDCl_3$): **6a**: $\delta = 3.85$ (d, 3H, $^3J_{P,H} = 7.2$ Hz, 3-Me); **6b**: $\delta = 4.73$ (d, 2H, $^3J_{P,H} = 5.8$ Hz, 3-CH_2); ^{13}C-NMR



5 **6**

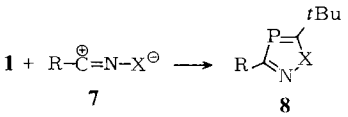
a: R = Me
b: R = CH_2–CN
c: R = CO_2Me
d: R = H
e: R = $SiMe_3$

Table 1. Yields, melting points, and characteristic NMR data of the phospholes **4**, **6**, and **8**.

Product	Yield [%][a]	M.p. [°C] B.p. [°C/mbar][b]	^{31}P-NMR [c]	^{13}C-NMR [d] C-3	C-5
4a	93	74	77.36	189.95 (61.26)	160.81 (59.09)
4b	92	122	75.32	191.37 (61.48)	173.39 (54.95)
4c	93	184	67.62	189.93 (60.50)	189.93 (60.50) [e]
4d	92	107	105.94	— [f]	— [f]
4e	86	135	97.58	192.13 (61.0)	164.91 (60.14)
4f	76	215	110.81	— [f]	— [f]
4g	82	78	90.51	185.07 (51.84)	190.85 (66.46)
4h	83	167	98.20	174.22 (47.3)	192.12 (64.1)
6a	91	$48/3 \times 10^{-3}$	173.48	—	198.25 (54.85)
6b	86	$72/3 \times 10^{-3}$	175.75	—	199.37 (55.15)
6c	92	41	177.06	—	200.60 (56.6)
6d	83	76	160.74	—	— [f]
6e	74	$50/10^{-3}$	183.18	—	— [f]
8a	67	42	76.94	179.87 (61.42)	226.53 (67.07)
8b	72	105	86.64	174.37 (54.43)	190.39 (57.21)

[a] After recrystallization from *n*-pentane (**4a—g**), tetrahydrofuran (**4h**), cyclopentane (**8b**), or kugelrohr distillation (**6a—e, 8a**); all compounds except **4h** (orange) are colorless and air-stable. [b] Oven temperature. [c] $CDCl_3$, 85% H_3PO_4 (ext.). [d] $CDCl_3$, TMS (int.) with $^1J(P,C)$ data [Hz] in parentheses. [e] The identity of both absorptions indicates electron delocalization in the ring and suggests rapid positional mobility of the hydrogen between the two nitrogen atoms. [f] Not measured.

($CDCl_3$): **6c**: $\delta = 151.3$ (d, $^2J_{P,C} = 22.0$ Hz, CO)]. It is, however, an open question as to which N atom of **6d** and **6e** the hydrogen and $SiMe_3$ group, respectively, is bonded.



7 **8**

	a	b
R	Mes	Ph
X	O	NPh

Finally the nitrile oxide and nitrilimine dipoles **7a** and **7b**, respectively, also undergo regiospecific [3+2]-cycloaddition to **1** to give the phospholes **8a** and **8b**; however, with the inverted dipole orientation. At least for **7a** this may stem from steric effects (Mes = mesityl). This can be unequivocally deduced from the ^{31}P-NMR signals of **8a** and **b** (Table 1), which lie in the same region as those of the diazoalkane adducts **4**.

Hydrogen chloride adds to benzylidynephosphane (P≡C–Ph), in contrast to nitriles, to afford benzylidene(chloro)phosphane[6]; cycloaddition of **2** and **5** to **1** proceeds analogously. The extraordinary tendency of phosphaalkynes **1** to undergo cycloadditions is comparable with that of the more electron-deficient acetylenes and differs markedly from the sluggishness of the nitrile group[7].

Procedure:

4e: A solution of **2e** (5.0 mmol) in 5 mL ether (anhydrous) is added dropwise to a solution of **1** (550 mg, 5.5 mmol) in 10 mL ether (anhydrous). At the end of the reaction (2 h, IR monitoring) the mixture is concentrated and the residue recrystallized at −30°C from *n*-pentane. Yield 860 mg (86%) colorless crystals of m.p. = 135°C.

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[1] As far as we know, only the reaction of α-pyrones and cyclopentadienones with chloro(α-trimethylsilylbenzylidene)phosphane and with the benzylidynephosphanes (P≡C–Ph) prepared from these in situ, respectively, leads to phosphinynes without the necessity of isolating the initial cycloadducts: G. Märkl, G. Yu Jin, E. Silbereisen, *Angew. Chem. 94* (1982) 383; *Angew. Chem. Int. Ed. Engl. 21* (1982) 370; *Angew. Chem. Suppl. 1982*, 881.
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[6] Cf. review article: R. Appel, F. Knoll, I. Ruppert, *Angew. Chem. 93* (1981) 771; *Angew. Chem. Int. Ed. Engl. 20* (1981) 731.
[7] See, for example: M. Regitz, H. Heydt in A. Padwa: *1,3-Dipolar Cycloaddition Chemistry*, Vol. 1, Wiley, New York 1984, p. 533ff.
[8] Note added in proof: 1,3-Dipolar cycloadditions to **1** see also Y. Y. C. Yeung Lam Ko, R. Carrié, A. Muench, G. Becker, *J. Chem. Soc. Chem. Commun. 1984*, in press.

1*H*-1,2,4-Diazaphospholes by [3+2]-Cycloaddition of Diazoalkanes to Phosphaalkenes

By *Gottfried Märkl** and *Irene Trötsch*

Cycloadditions to open-chain, non-resonance stabilized phosphaalkenes are attracting increasing interest. We were recently able to show that chloro(α-trimethylsilylbenzylidene)phosphane (1-chloro-2-phenyl-2-trimethylsilyl-1-

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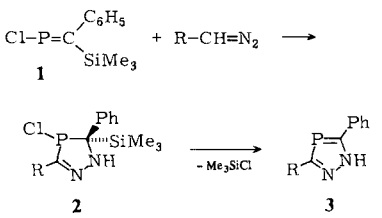
phosphaethane) **1**[1] reacts as a dienophile with α-pyrones and cyclopentadienones via [4+2]-cycloadditions to give phosphinines (intermediate formation of 2-phenyl-1-phosphaethyne (P≡C–Ph) cannot be ruled out)[2]. *Appel* et al.[3] have since reported on the Diels-Alder reaction of 1-alkoxy-2-phenyl-2-trimethylsilyl-1-phosphaethene with 2,3-dimethylbutadiene, while 1-mesityl-2,2-diphenyl-1-phosphaethene—presumably for steric reasons—no longer reacts as dienophile[4].

The first [8+2]-cycloaddition of **1** to 8-methoxyheptafulvene provided access for the first time to a 2-phosphaazulene derivative[5]. [3+2]-Cycloadditions of PC double bonds in 1,2,3-diazaphospholes with 1,3-dipoles (diazoalkanes[6], nitrile oxides[7], nitrile imines[8], azides[9]) have been the subject of numerous studies in recent years.

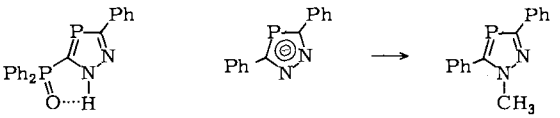
The dipolarophile-reactivity of the phosphaalkanes is—presumably because of the polarity of the P=C bond—much more pronounced than their diene reactivity. According to *Bickelhaupt* et al.[4], 1-mesityl-2,2-diphenyl-1-phosphaethene reacts with phenyl azide and with diphenyldiazomethane to give 4,5-dihydro-1,2,3,4-triazaphospholes and 4,5-dihydro-1,2,3-diazaphospholes, respectively.

We have now found that diazoalkanes almost instantaneously undergo [3+2]-cycloaddition with phosphaalkenes **1**, even at room temperature. The cycloadducts **2** expected to be formed initially aromatize under the reaction conditions by spontaneous elimination of trimethylchlorosilane to give the 1*H*-1,2,4-diazaphospholes **3** with triple-bonded phosphorus of coordination number two (see Table 1).



1 **2** **3**

The regioselectivity of the cycloaddition corresponds to the polarity of the P=C bond. Whereas all formally possible 1,3,2-, 1,3,4- and 1,2,3-diazaphospholes are already known, the 1,2,4-diazaphospholes have hitherto remained inaccessible. The synthesis of this novel ring system has now been accomplished by *Regitz* et al.[10] by [3+2]-cycloaddition of diazoalkanes to the phosphaethyne P≡C–*t*Bu and, at the same time, by *Schmidpeter* et al.[11] by cyclization of 1,3-bis(dimethylamino)-2-phosphaallyl chlorides with hydrazines.



3g′ **4b** **5**

The spectroscopic data of **3** are consistent with the proposed structure (^{31}P-NMR: $\delta = +75.9$ to $+113.4$, Table 1). The broad absorption bands for the NH stretching vibration point to the formation of hydrogen bridges; in the case of **3c**—**g** the presence of the tautomers **3′** with intramolecular H-bridges, e.g. **3g′**, cannot be ruled out. The position and splitting of the P=O stretching vibrations in the IR spectra also lend support to this assumption[12]. Reaction of **3** with *n*BuLi in tetrahydrofuran at −78 °C leads to formation of the phosphole anions **4**; on treatment with methyl iodide, the symmetrical **4b** is alkylated to the 1-methyl-3,5-diphenyl-1,2,4-diazaphosphole **5** (m.p. 104—106 °; ^{31}P-NMR: $\delta = 88.7$)[11].

The cycloaddition of the phosphaalkenes as dipolarophiles to 1,3-dipoles is not restricted to **1**. In preliminary

Table 1. Properties and spectroscopic data of the 1,2,4-diazaphospholes **3**. ^{1}H- and ^{31}P-NMR in $CDCl_3$, δ-values, *J* [Hz].

Compd. R	Yield [%]	M.p. [°C]	IR (KBr [cm^{-1}]) ν(NH)	ν(C=O)	ν(P=O)	^{1}H-NMR R	C_6H_5	^{31}P-NMR	MS (70 EV), *m/z*
3a	46	≈40	3205	—	—	8.53 (d), *J*(PH) = 40.0	7.23 (t), 3H; 7.73 (m), 2H	81.4, *J*(PH) = 41.6	$M^{\oplus}$ 162 (100%); $[M-HCN]^{\odot\oplus}$ 135 (16%); $[Ph-C\equiv P]^{\odot\oplus}$ 120 (3%); $[PhC\equiv NH]^{\oplus}$ 104 (23%)
3b [11]	62	200 [a]	3190	—	—	7.17—8.23 (m)		+ 75.9	$M^{\odot\oplus}$ 238 (100%); $[M-PhCN]^{\oplus}$ 135 (14%); $[PhP]^{\odot\oplus}$ 108 (24%)
3c COOEt	90	156—159 [b]	3195	1705	—	1.37 (t), 4.37 (q), *J*(HH) = 7.0	7.50 (t), 3H; 7.97 (m), 2H	+ 98.6	$M^{\odot\oplus}$ 252 (93%); $[M-{}^{\odot}CH_3]^{\oplus}$ 237 (85%); $[M-{}^{\odot}C_2H_5]^{\oplus}$ 223 (72%); $[M-{}^{\odot}PhCN_2]^{\oplus}$ 135 (100%)
3d COPh	35	142	3180	1645	—	7.23—7.53 (m), 6H; 7.73—7.93 (m), 2H; 8.00—8.20 (m), 2H		105.0	$M^{\odot\oplus}$ 266 (100%); $[M-PhCN]^{\odot\oplus}$ 163 (21%); [PhC=O] 105 (87%)
3e [c] $(MeO)_2P(O)$	82	128—132	3105, 3140	—	1175, 1210, 1225, ν(P–OMe) 1030	4.05 (d), *J*(PH) = 12	7.43—7.67 (m), 3H; 7.97—8.23 (m), 2H	+ 111.1 (d), + 27.4 (d), *J*(PP) = 65.0	$M^{\odot\oplus}$ 270 (100%); $[M-{}^{\odot}PhCN_2]^{\oplus}$ 153 (40%); $[(MeO)_2P=O]^{\oplus}$ 109 (23%) [d]
3f [c] MeO(Ph)P(O)	84	115 [b]	3020, 3070	—	1175, 1210, 1225, 1235, ν(P–OMe) 1030	3.92 (d), *J*(PH) = 12	7.17—7.53 (m), 6H; 7.67—8.13 (m), 4H	+ 111.1 (d), + 27.4 (d), *J*(PP) = 55.8	$M^{\odot\oplus}$ 316 (64%); $[M-{}^{\odot}PhCN_2]^{\oplus}$ 199 (19%); $[Ph(MeO)P=O]^{\oplus}$ 155 (100%) [d]
3g [c] $Ph_2P(O)$	80	215	3010, 3025, 3040	—	1165, 1185	7.33—8.20 (m)		+ 113.4 (d), + 23.4 (d), *J*(PP) = 53	$M^{\odot}$ 362 (8%); $[M-{}^{\odot}PhCN_2]^{\oplus}$ 245 (2%); $[M-PC(Ph)N_2]$ 214 (8%); $[Ph_2PO]^{\oplus}$ 201 (100%)

[a] Baked at 160 °C; at 200 °C, a viscous brown film is formed. [b] Viscous brown film. [c] We thank Prof. Dr. *M. Regitz* and Doz. Dr. *G. Maas* for gifts of the appropriate diazoalkanes. [d] The $[M+CH_2]^{\odot\oplus}$ signals occurring along with $M^{\odot\oplus}$ lend support for a thermally induced intermolecular *N*-methylation in the inlet system of the mass spectrometer.

experiments we could show that 1-chloro-2,2-bis(trimethylsilyl)-1-phosphaethene[13] also undergoes [3+2]-cycloaddition with diazoalkanes. **1** also reacts with azides, nitrile imines, and nitrile oxides.

Experimental

3d: **1** (1.60 g, 7.00 mmol) was treated with a solution of benzoyldiazomethane (1.00 g, 6.8 mmol) in anhydrous ether (10 mL) at 0°C under pure nitrogen in a 25 mL flask fitted with a capillary side-arm and stopcock. The solution slowly turned dark brown. After stirring for 3 h at room temperature the solvent was removed and the viscous, dark residue dissolved in chloroform and treated with *n*-pentane. **3d** separated from the solution as a brown powder, which could be purified by distillation from a microdistillation apparatus at 10^{-5} torr. **3d** distilled off as a bright yellow oil which rapidly crystallized; pale yellow crystals, m.p. 142°C (from ethyl acetate/pentane), yield 0.65 g (35%).

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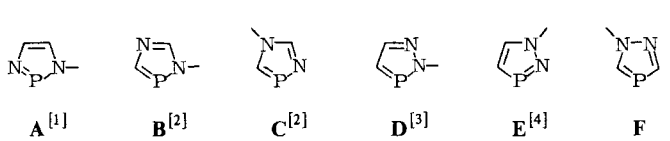
1*H*-1,2,4-Diazaphospholes via 2-Phosphaallyl Chlorides**

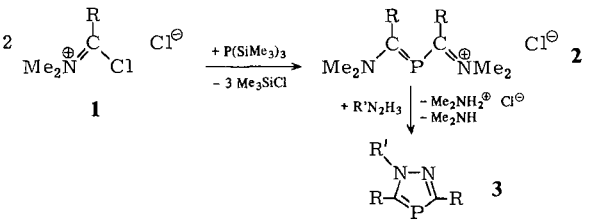
By *Alfred Schmidpeter** and *Angela Willhalm*

Of the diazaphospholes **A**—**F**, five (**A**—**E**) contain at least one PN bond and can be synthesized by condensing phosphorus in the form of PCl_3 or $ClCH_2PCl_2$ onto a chain with a terminal amino group.

Diazaphospholes of the still outstanding type **F** are not accessible via a comparable route. In terms of the bonding situation of the phosphorus, they should correspond to the phosphinyines (phosphabenzenes) and thus lead one to expect a behavior different to that observed in the other isomers. Condensation of 1,3-bis(dimethylamino)-2-phosphaallyl chlorides **2** with hydrazines now opens up a general approach to 1*H*-1,2,4-diazaphospholes **3** (**F**). An additional synthetic pathway to substituted derivatives of **F** is the cycloaddition of diazoalkanes to a phosphaethyne[5] or to a 1-chloro-2-trimethylsilyl-1-phosphaethene with spontaneous elimination of trimethylchlorosilane[6].



A[1] **B**[2] **C**[2] **D**[3] **E**[4] **F**



1 **2** **3**

Reaction of salts derived from imidoyl chlorides **1** with tris(trimethylsilyl)phosphane, a method described previously for tetrakis(dimethylamino)-2-phosphaallyl chloride **2f**[7], permits the synthesis of further phosphaallyl chlorides **2** in almost quantitative yield[8]. These are stable compounds which are not sensitive towards oxidation and hydrolysis and, depending on the substituents R, are yellow to red-brown crystalline solids (Table 1). Their ^{31}P-NMR shifts extend over a remarkably large range $\Delta\delta(^{31}P) = 210$[7].

Table 1. Properties and ^{31}P-NMR data of 2-phosphaallyl chlorides **2** and 1,2,4-diazaphospholes **3**. The diazaphospholes **3d**, **e** are colorless liquids; **3h** is a colorless oil which cannot be distilled.

	R′	R	Color of the crystals	M.p. [°C] B.p. [°C/torr]	$\delta(^{31}P)$ (J(PCH) [Hz])
2a		H	straw yellow	135—136	41.7 [g] (t, 9.5)
2b		*t*Bu	orange-red	137—139	34.0 [g]
2c		*c*Hex	light orange	124—126	16.4 [g]
2d		Ph	orange	193—195	113.0 [g]
2e		$pNO_2C_6H_4$	red-brown	122—124	117.0 [g]
2f [7]		NMe_2	yellow	193—195	−21.9 [g]
2g		SMe	orange	142—144	44.6 [g]
3a	H	H [a]	colorless	77—78	82.8 [h] (t, 44.1)
3b [5]	H	*t*Bu [b]	colorless	180—181	65.4 [h]
3c [6]	H	Ph [a]	colorless	214—217	74.3 [h]
3d	Me	H [a]	colorless	60/15	92.3 [i] (dd, 47.5, 39.7)
3e	Me	*t*Bu [e]	colorless	40/0.02	82.5 [h]
3f [6]	Me	Ph [b]	pale yellow	105—108	89.3 [h]
3g	Ph	H [c]	colorless	33—34	99.4 [h] (dd, 47.5, 39.3)
3h	Ph	*t*Bu [d]	colorless		82.7 [h]
3i	Ph	Ph [f]	yellow	201—203	95.1 [k]

Synthetic conditions [8]: [a], [b] in chloroform, RT, 5 min and 12 h, resp.; [c], [d] in chloroform, reflux, 5 h and 10 d, resp.; [e], [f] in chlorobenzene, 95°C, 4 h and 1 d, resp.—Solvent: [g] acetonitrile, [h] chloroform, [i] dichloromethane, [k] chlorobenzene.

The cyclization of the phosphaallyl chlorides was studied using **2a**, **b**, **d** as examples. These compounds react completely with hydrazine and methyl hydrazine at room temperature and with phenyl hydrazine at 60—100°C to afford the 1*H*-1,2,4-diazaphospholes **3**[8,9]. The reaction rate decreases along the series R = H, Ph, *t*Bu; **2f**, R = NMe_2, does not react. The 1,2,4-diazaphospholes **3** (like azaphospholes in general) are not oxidized by atmospheric oxygen; in contrast to their isomers of the type **A**—

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E, they are also not hydrolyzed by conc. hydrochloric acid. **3a**—**c** can be deprotonated with sodium hydroxide and acylated at the nitrogen.

Although in the 1,2,4-diazaphospholes a 1,3-diamino-2-phosphaallyl system is still formally present, the ring closure is associated with an essential change: the color fades, the effect of R on $\delta(^{31}P)$ decreases, and J_{PCH} increases considerably (to around 40 Hz, the normal value for phosphaarenes[4]). These correspond to a change from the (presumed) *cis,cis*-position of the hydrogen in **2a** to the *trans,trans*-position in **3a**, **d**, **g** governed by the ring[10]. As in pyrazoles[11], the hydrogen atom on the nitrogen in **3a-c** exchanges between the two N atoms so rapidly that the compounds appear symmetrical and, e.g., **3a** exhibits two identical (averaged) PCH couplings (Table 1).

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[8] General procedure. **2**: $P(SiMe_3)_3$ (50 mmol) is added dropwise over 45 min to **1** (100 mmol) in 200 mL anhydrous acetonitrile. After 10 h at room temperature the solution is concentrated and the residue washed several times with ether; 80—96% yield.—**3**: The particular hydrazine (10 mmol) is added to a solution of **2** (10 mmol) in 30 mL solvent. After completion of the reaction (see Table 1), the solvent is removed, the residue digested with 30 mL ether, the suspension formed filtered through a fine-pore frit after 1—2 d at room temperature, and the filtrate concentrated. The residue consisting of **3** is dried, distilled (**3d**, **e**), or sublimed (**3g** at 20°C/0.001 torr); 40—98% yield.

[9] For a corresponding condensation of 1,3-bis(dimethylamino)allyl(vinamidinium) perchlorates with hydrazine and phenyl hydrazine to afford pyrazoles, see: R. Gompper, R. Sobotta, *Synthesis 1979*, 385.

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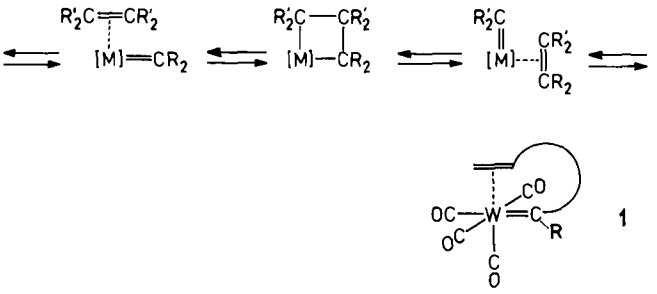
Synthesis and Structure of a (Carbene)(η^2-olefin)$W(CO)_4$ Complex

By *Klaus Angermund, Friedrich-Wilhelm Grevels*, Carl Krüger,* and *Volker Skibbe*

According to a generally accepted reaction mechanism[2], carbene(olefin) and metallacyclobutane complexes participate as reactive intermediates in transition metal-catalyzed olefin metathesis[1]. As model compounds, $W(CO)_4$ complexes of the type **1** were synthesized[3,4] in which a carbene(olefin) chelate ligand occupies two *cis*-positions. The stability of these compounds and the orientation of the carbene and the olefin groups—which is of importance for a ring closure to the metallacyclobutane[5]—are strongly influenced by the chelate ring.



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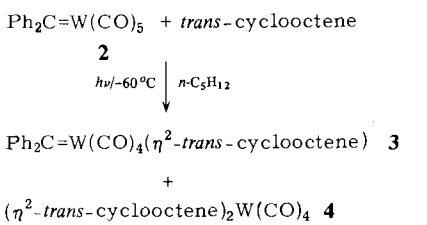
We have now synthesized a (carbene)(η^2-olefin)$W(CO)_4$ complex without recourse to a stabilizing chelate ligand. The photochemical reaction of the carbene complex **2**[6] in *n*-pentane at −60°C with *trans*-cyclooctene, which proved to be a good coordinating ligand in the preparation of the first (η^2-olefin)$_2Cr(CO)_4$ complex[7], affords the carbene(olefin) complex **3**[8] as major product; small amounts of the bis(olefin) complex **4** are formed concomitantly[10]. Although complex **3** is stable at room temperature in apolar solvents such as *n*-hexane or toluene, work-up and purification of the crude product is recommended to be performed with cooling.



On attempting to introduce the two organic ligands in the reverse sequence using $W(CO)_6$ as starting substance, we obtained pentacarbonyl(η^2-*trans*-cyclooctene)tungsten **5**[11] in the first step. However, attempts to convert a carbonyl group of **5** into a carbene ligand by the usual method[12] failed.

The IR spectrum of **3** shows four bands [2057.5 (w), 1997.5 (w), 1970.5 (vs), 1962 (vs) cm^{-1}; *n*-hexane] in the CO stretching vibration region, which could be indicative of a *cis* arrangement of the carbene and the olefin ligand. The relative intensities of these bands, however, point to an almost square-planar $W(CO)_4$ unit with two *trans* oriented organic ligands[13].

The X-ray structure analysis of **3** (Fig. 1) confirms that the olefin and the carbene ligands occupy *trans* positions on the octahedrally coordinated tungsten; the C13, C14, C15 plane of the carbene and the C=C axis of *trans*-cyclooctene are almost coplanar. Thus, the metal→ligand back-bondings became as strong as possible: because of the almost orthogonal disposition of their π-acceptor orbitals, the organic ligands can employ *two* metal d-orbitals for the back-bonding, and there is no competition with a *trans*-oriented CO group.

The bonding situation in *trans*-(η^2-olefin)$_2ML_4$ complexes is explained in much the same way[13,14]. Such an arrangement of two "single-faced" ligands is always to be expected when π back-bonding contributes substantially to the metal-ligand bond; chelate ligands can, however, command a different geometry.

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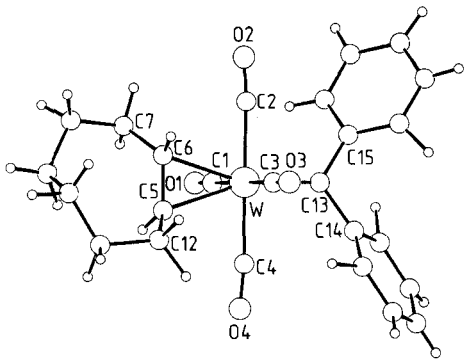
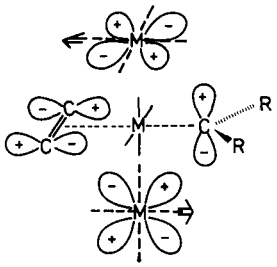


Fig. 1. Structure of **3** in the crystal. $P\bar{1}$, $a = 12.193(2)$, $b = 13.359(1)$, $c = 7.0813(7)$ Å, $\alpha = 93.469(7)$, $\beta = 106.873(8)$, $\gamma = 89.017(8)°$, $Z = 2$, $\rho_{ber.} = 1.73$ g cm^{-3}; $\lambda = 0.71069$ Å, $\mu = 53.8$ cm^{-1} (analytical absorption corrections), $R = 0.030$, $R_w = 0.038$; 6706 reflections observed [$I > 2\sigma(I)$], 1512 reflections unobserved; 271 refined parameters; maximal residual density 2.56 eÅ^{-3} (on W). The planes through the atoms W, C5, C6 and the compensating planes through W, C13, C14, C15 form an angle of 8.8°. Selected bond lengths [Å] and bond angles [°]: W-C1 2.072(4), W-C2 2.064(4), W-C3 2.078(4), W-C4 2.055(4), W-C5 2.341(4), W-C6 2.341(4), W-C13 2.067(4), C1-O1 1.138(6), C2-O2 1.131(5), C3-O3 1.134(6), C4-O4 1.142(5), C5-C6 1.389(6); C6-W-C13 162.7(1), C5-W-C13 162.8(1), torsion angle C12-C5-C6-C7 −125.4. Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD 50970, the names of the authors, and the journal citation.

Metallacyclobutane ring closure is not possible in the case of *trans*-oriented olefin and carbene ligands, so it is not surprising that metathesis catalysts usually contain the metal in a higher oxidation state. In these systems the π



back-bonding is weaker and thus its directing influence, smaller. It therefore appears questionable whether carbonylmetal(0) complexes of the type **1** are realistic models for olefin metathesis.

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[8] *Experimental.* **3**: A solution of **2** (0.22 g, 0.45 mmol) and *trans*-cyclooctene [9] (0.22 g, 2 mmol) in *n*-pentane (220 mL) was irradiated for 1 h at −60° (immersion apparatus of solidex glass with cooling jacket, Philips HPK 125W mercury vapor lamp), whereupon the color of the solution changed from deep-red to orange. After removal of the solvent the crude product was chromatographed on silica gel at −25°C. **4** and residual **2** were first eluted with *n*-pentane, then **3** with diethyl ether/*n*-pentane (1:50). The crude **3** recovered after removal of solvent was recrystallized at 20°C/−78°C from 3 mL toluene (0.10 g, 39%); orange crystals, m.p. 135°C (decomp.). ^{1}H-NMR ([D$_8$]toluene): $\delta = 0.91$ (4H), 1.42 (2H), 1.86 (4H), 2.67 (4H), 7.1 (10H).

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[11] **5**: colorless crystals, m.p. 69°C. IR (*n*-hexane): ν(CO) = 2079.5 (w), 1967 (s), 1955 (m), 1948 (s) cm^{-1}. ^{1}H-NMR ([D$_8$]toluene): $\delta = 0.54$ (2H), 0.95 (2H), 1.26 (2H), 1.63 (4H), 2.49 (2H), 3.54 (2H).

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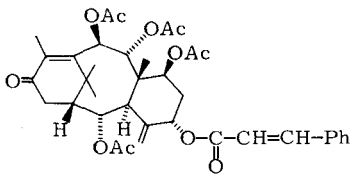
A Novel Entry to the Taxane Structural Unit**

By *Harribert Neh, Siegfried Blechert*, Wolfgang Schnick,* and *Martin Jansen*

Taxanes, such as, e.g., taxinin B **1** or taxol **2**, are unusual hydroxylated diterpenes which occur in plants of the family Taxaceae, to which the yew tree *(Taxus baccata L.)* belongs[1]. The antileukemic and antitumoral activities of some taxanes[1] and the problems encountered in the synthesis of the unusual tricyclic carbon skeleton **3** have aroused increasing interest in recent years[3]. According to in vitro experiments[4], less substituted taxane derivatives could also be biologically active. For this reason it appeared to us that the synthesis of a tricyclic taxane skeleton with functional groups in ring A and ring B which should be readily convertible into hydroxy groups might prove rewarding. We report here on a stereoselective route to the tricycle **4**.



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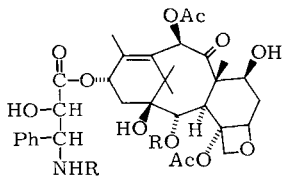
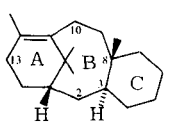


2, R = COPh



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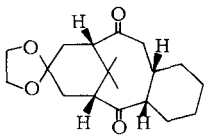

4

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[+] X-Ray structure analysis.

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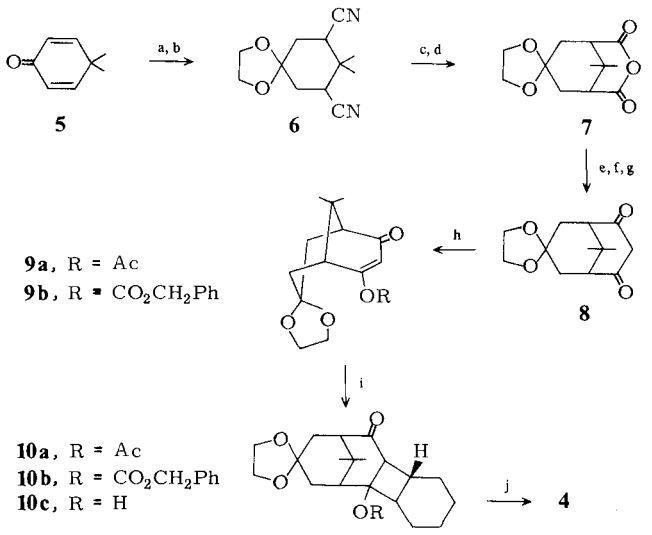
A problem in the synthesis of the taxane framework is the formation of the eight-membered ring. This has previously been achieved by way of intramolecular Diels-Alder reactions, but this approach involved an aromatic ring C[5] or simply dispensed of the bulky geminal dimethyl group[6]. For preparation of the central ring, we used the de Mayo reaction[7,8]. The key step of our reaction sequence **5**→**4** (Scheme 1) is the stereoselective [2+2]-photocycloaddition of cyclohexenes to the bicycle **9**, since in this way the configuration at C-8 of the taxane framework is fixed. A C-8-α-ring coupling should be possible by a β-*exo* attack of the cyclohexene. As directing substituent we chose a ketal, which we expected would, according to model considerations, favor the formation of a β-adduct.



Scheme 1. a) KCN, NH_4Cl, $(DMF)/H_2O$, 68% yield; b) $HOCH_2CH_2OH$, *p*-toluenesulfonic acid, benzene, 83% yield; c) KOH, H_2O_2/H_2O, 3 d reflux, yield 88%; d) dicyclohexylcarbodiimide, CH_2Cl_2, 91% yield; e) MeLi, −60°C, 55% yield; f) CH_2N_2, 95% yield; g) KH, xylene, reflux, 85% yield; h) Ac_2O/NaOAc, 96% yield or $ClCO_2CH_2Ph$, CH_2Cl_2, aq. $NaHCO_3$, 86% yield; i) cyclohexene/CH_2Cl_2, hv, −78°C, **10a**: 56% yield +15% educt, **10b**: 65% yield +30% educt; j) 0.5 N KOH/EtOH, 15 h, 56% yield.

Our strategy for the synthesis of the 1,3-diketone **8** enabled us to investigate intramolecular photocycloadditions also, since substituted 1,3-diketones can be synthesized from the anhydride **7** by reactions with alkyllithium compounds other than MeLi. Irradiation of the enol acetate **9a** (500 W Hg high-pressure lamp (Pyrex filter), 4 h, −78°C) in a 4:1 mixture of dichloromethane/cyclohexene led to **10a**, which, however, was less suited for the ring-opening, since elimination readily takes place with formation of cyclobutene. The benzyl carbonate **10b**, which is obtainable in 65% yield (30% recovered educt) from **9b** after chromatography can, on the other hand, be converted quantitatively by hydrogenolysis (H_2, Pd/C) into the alcohol **10c**. The very slow retroaldol cleavage leading to formation of **4** (15 h, 0.5 N ethanolic KOH solution) is remarkable. After chromatography on silica gel, during which larger losses occur, the diketone **4** is obtained in 56% yield (m.p. 129—130°C, crystallization from petroleum ether). The configuration at C-3 and C-8 could not be determined unequivocally on the basis of the NMR data[9] in the case of the strongly strained tricycle **4**; however, this could only be established by X-ray structure analysis[10].

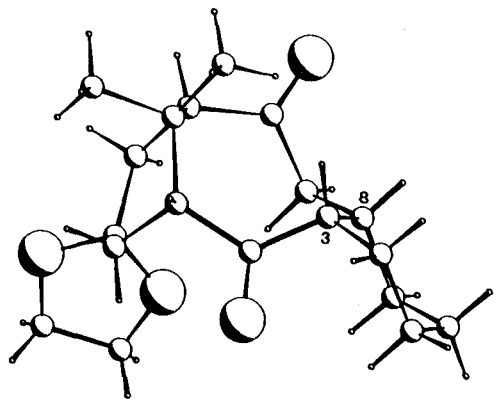


Fig. 1. Structure of a molecule of **4** in the crystal (PLUTO-PLOT).

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4, 92695-04-0; **5**, 1073-14-9; **6**, 92694-96-7; **7**, 92694-97-8; **8**, 92694-98-9; **9a**, 92694-99-0; **9b**, 92695-00-6; **10a**, 92695-01-7; **10b**, 92695-02-8; **10c**, 92695-03-9; $HOCH_2CH_2OH$, 107-21-1; cyclohexene, 110-83-8.

[1] Review: R. W. Miller, *J. Nat. Prod. 43* (1980) 425.
[2] M. C. Wani, M. L. Taylor, M. E. Wall, P. Coggon, A. T. McPhail, *J. Am. Chem. Soc. 93* (1971) 2325.
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[4] V. Senilh, Dissertation, Université de Paris-Sud, Centre D'Orsay 1984.
[5] K. J. Shea, P. D. Davis, *Angew. Chem. 95* (1983) 422; *Angew. Chem. Int. Ed. Engl. 22* (1983) 419; *Angew. Chem. Suppl. 1983*, 564.
[6] P. A. Brown, P. R. Jenkins, J. Fawcett, D. R. Russell, *J. Chem. Soc. Chem. Commun. 1984*, 253.
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[9] Supplementary ^{1}H-NMR data (400 MHz, $CDCl_3$): $\delta = 3.8-4.2$ (ketal-H, m), 3.71 (H_α-9, t, $J = 12.2$ Hz), 3.41 (H-3, t d, $J = 5.0$ and 1.2 Hz), 2.98 (H_α-14, ddd, $J = 12.8$, 4.8, and 1.8 Hz), 2.48 (H-11, d (br.), $J = 7.5$ Hz), 2.32 (H_β-12, dd, $J = 16.2$ and 7.8 Hz), 2.05—2.13 (H_β-14, H-1, H-8, m), 2.01 (H_α-12, dd (br.), $J = 16$ and 2 Hz), 1.97 (H_β-9, ddd, $J = 12.4$, 6.0, and 1.8 Hz), 1.75 (1 H, m), 1.67 (1 H, m), 1.1—1.5 (6 H, m), 1.31 (3 H, s), 1.45 (3 H, s).
[10] $4 = C_{19}H_{28}O_4$, $M_r = 320.4$; $a = 6.737$, $b = 9.971$, $c = 14.114$ Å, $\alpha = 69.37$, $\beta = 83.98$, $\gamma = 86.04$, $V = 881.9$ Å^3, $Z = 2$, space group $P\bar{1}$. Data collection: Siemens AED2 diffractometer, $Mo_{K\alpha}$ radiation, graphite monochromator, scan width 1.2°, ω-scan, 8080 measured reflections in the range $3.1° < 2\theta < 50.0°$, 1723 symmetry independent reflections with $F > 3\sigma(F)$, solution of structure by direct methods. Anisotropic refinement of all atoms other than hydrogen, hydrogen atoms isotropic, $R = 0.0624$ for 208 free parameters, $R_w = 0.0467$, $W = 2.833/[\sigma^2(F)]$. Further details of the crystal structure are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD 51050, the names of the authors, and the journal citation.

$Ag_{1.8}Mn_8O_{16}$: Square Planar Coordinated $Ag^{\oplus}$ Ions in the Channels of a Novel Hollandite Variant**

By *Fung Ming Chang* and *Martin Jansen**

Compounds crystallizing in the hollandite structure (idealized formula $A^{n\oplus}_{(2/n-x)}B_8O_{16}$, n = 1, 2) are currently the subject of numerous studies in the field of solid-state

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chemistry[1]. The great amount of interest being shown in these compounds is due to their zeolite-like structure, their possible use as a matrix for the disposal of nuclear waste (^{137}Cs), and as ionic conductors. Furthermore, the hollandite structure is of geochemical significance as a high-pressure form of the feldspars. Hence, it is not surprising that detailed expositions have already been published on the systematic structural classification of this type of structure, and quite clear concepts have so far been presented (and in each case confirmed) about its range of existence as a function of the effective radii of the monovalent and divalent cations A[1b]. During investigations on the thermal degradation of $AgMnO_4$ we obtained $Ag_{1.8}Mn_8O_{16}$, the first compound with hollandite structure which lies outside this range.

$Ag_{1.8}Mn_8O_{16}$ is formed from a mixture of $AgMnO_4$ and Ag_2O in the molar ratio 1:1 at 970°C under 5 kbar oxygen (stainless steel autoclave) within 7 d. Under these conditions $Ag_{1.8}Mn_8O_{16}$ already separates out in coarsely crystalline form (needle-like crystals, maximum dimensions $0.1 \times 0.4 \times 1.0$ mm^3). The by-products, Mn_2O_3 and Ag_2O, can be removed by successive treatment with semiconcentrated nitric acid and dilute hydrochloric acid; $Ag_{1.8}Mn_8O_{16}$ is not attacked by these acids during short periods of reaction.

The complete X-ray structure analysis[2] shows that a Mn_8O_{16} skeletal framework of corner- and edge-sharing MnO_6 octahedra is present in the new compound, which compares in all essential structural features with the corresponding structural unit in $Ba_{1-x}Mn_8O_{16}$, the prototype of this substance class. The channel-like cavities (along [001]) of this skeletal unit consist of cubes coupled via common opposite faces. Surprisingly, the silver atoms do not occupy the centers, but rather the common faces of these cubes (Fig. 1). This leads to unusual square-planar coordination, observed here for the first time, for $Ag^{\oplus}$. A higher oxidation state (2+ or 3+) of silver (with corresponding charge compensation in the Mn_8O_{16} sublattice), for which this coordination would be characteristic, can be ruled out on the basis of the observed bond lengths (Ag–O: 244, in Ag_2O_3[3], e.g., 202 pm). Other than in almost all cases[4], the lattice sites available for $A^{n\oplus}$ ions are, to a large extent, occupied[5]. We ascribe both these peculiarities to a pronounced adaptability of monovalent silver to a given matrix. In oxo compounds $Ag^{\oplus}$ can deviate from the linear double coordination with formation of atypical surroundings with coordination numbers three or four[6]; the short distances between the positions A, which frequently preclude their complete occupation, are, according to recent findings[7], unproblematical in the case of $Ag^{\oplus}$.

As a consequence of the above results, the region of existence of the hollandite structure must be redefined, and arguments regarding the influence of the size of the $A^{n\oplus}$ ion on symmetry-lowering distortions[1b] of the B_8O_{16} framework must be reconsidered.

Hollandites are model substances for the study of one-dimensional ionic conductors. In $Ag_{1.8}Mn_8O_{16}$, the repulsive forces (Born repulsion) on passage of $Ag^{\oplus}$ through a face of its coordination polyhedron, which otherwise are to be overcome during migration of ions in a solid, cannot occur because the silver ions occupy the narrowest siges of the one-dimensional diffusion channels as regular lattice sites. An especially low activation is to be expected for the ionic conduction.

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CAS Registry numbers:
$Ag_{1.8}Mn_8O_{16}$, 57176-38-2; $AgMnO_4$, 7783-98-4; Ag_2O, 20667-12-3.

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[2] Tetragonal, I4/m, $a = 972.5(7)$, $c = 288.5(2)$ pm, $Z = 1$, Siemens AED2 four-circle diffractometer, $Mo_{K\alpha}$, graphite monochromator, 314 independent reflections with $I > 3\sigma(I)$, $R = 0.061$; Atomic distances [pm]: Mn-O1 193.9(6), Mn-O'1 195.1(9), Mn-O2 189.1(5), Mn-O'2 187.1(9), Ag-O1 243.7(9), Ag-Ag 288.5(2); Mn atoms not shown in Figure 1. Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD 51049, the names of the authors, and the journal citation.

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[6] M. Jansen, *Acta Crystallogr. Sect. B 33* (1977) 3584.

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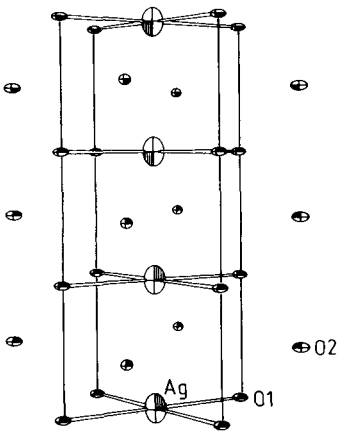

Fig. 1. Section from the structure of $Ag_{1.8}Mn_8O_{16}$: silver ions in the channels.

A Novel Iron-Sulfur Cluster with Central Fe_8-Cube: Synthesis and Structure of $(Et_4N)_3Fe_8S_6I_8 \cdot 2\,CH_2Cl_2$**

By *Siegfried Pohl** and *Wolfgang Saak*

Concomitant with the synthesis of a series of iron-sulfur clusters[1-5] in the last few years, models have also been developed for the synthesis of the active center of the FeMo protein of nitrogenase[3,6]. Starting from $(Et_4N)_2Fe_6S_6I_6$[4], we were able to synthesize according to the equation

$$Fe_6S_6I_6^{2\ominus} + 2\,Fe + I^{\ominus} + 1/2\,I_2 \xrightarrow{CH_2Cl_2} Fe_8S_6I_8^{3\ominus}$$

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a novel Fe–S cluster, whose skeletal structure very closely approaches these model concepts. $Fe_8S_6I_8^{3\ominus}$ was isolated as the salt $(Et_4N)_3Fe_8S_6I_8 \cdot 2CH_2Cl_2$ **1**, which crystallizes in the form of black octahedron. According to an X-ray structure analysis **1** contains discrete $Fe_8S_6I_8^{3\ominus}$ cluster anions (Fig. 1), which, with crystallographic C_{2h} symmetry, exhibit almost O_h symmetry. The eight iron atoms with FeFeFe angles of 90° and Fe–Fe distances of 270.4(8)–273.3(9) pm form an almost ideal cube. With the six sulfur atoms μ_4-bonded over the faces of the cube (Fe–S distances: 230.9(9)–233.2(10) pm) this gives an almost regular dodecahedral array of twelve quadrilateral faces. Hence, with respect to the terminal iodine atoms, this results in a slightly distorted tetrahedral arrangement of the iron atoms with angles between 107.5(5) and 112.6(3)°. The formal oxidation state for all iron atoms is +2.125. We assume that the corresponding fourfold negatively charged cluster, in which the iron atoms would be exclusively divalent, could likewise be prepared on modification of the synthesis conditions; an analogous thiolate-substituted Co cluster has already been described[6].

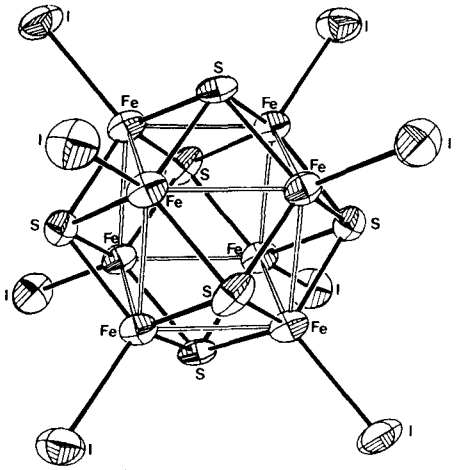

Fig. 1. Structure of the anion $Fe_8S_6I_8^{3\ominus}$ in the crystal of **1**; vibration ellipsoids with 50% probability. Structural data: C2/m, $a = 1707.3(4)$, $b = 2269.4(7)$, $c = 1206.1(2)$ pm, $\beta = 135.22(2)°$, $Z = 2$; 1612 symmetry-independent reflections, 947 observed ($I > 1.96\sigma(I)$); $R_w = 0.072$. Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD 51081, the names of the authors, and the journal citation.

According to our investigations on the redox system $Fe/I_2/S/I^{\ominus}$, which previously led to the synthesis of the cluster anions $Fe_2S_2I_4^{2\ominus}$, $Fe_4S_4I_4^{2\ominus}$[7], $Fe_6S_6I_6^{2\ominus}$[4], and now also to $Fe_8S_6I_8^{3\ominus}$, ligand deficiency for the iron atoms is a prerequisite for the formation of a Fe_8S_6 cluster with exclusively μ_4-bonded sulfur. Thus, we could previously only isolate **1** from CH_2Cl_2, a solvent which does not function as a coordinating entity towards Fe. Consistent with this concept, excess sulfur is reduced by iron in the complex, i.e. made available as ligand, with the result that the Fe_8S_6 cluster is converted into products such as $Fe_6S_6I_6^{2\ominus}$ or $Fe_4S_4I_4^{2\ominus}$ containing μ_3-bonded sulfur.

Replacement of an iron atom in the Fe_8S_6 cluster by molybdenum furnishes an atomic ratio which corresponds to that in the FeMo cofactor of *Azobacter vinelandii*[8,9] (cf. also [3]). The synthesis of **1** is thus probably an essential step en route to a compound which can be described as a model substance in the context of the above-mentioned investigations.

Experimental

All operations were carried out under nitrogen in anhydrous, oxygen-free solvents. A suspension of Fe (0.06 g, 1.07 mmol), Et_4NI (0.13 g, 0.52 mmol), and I_2 (0.07 g, 0.27 mmol) in CH_2Cl_2 (60 mL) was heated for 24 h at room temperature. After addition of 1.0 g (0.52 mmol) $[Et_4N]_2Fe_6S_6I_6$, the suspension was repeatedly heated to ca. 60°C in a sealed flask (under pressure). The amorphous precipitate that was formed partly converted into crystalline **1** on being allowed to stand for several weeks at room temperature. The well-formed crystals could be mechanically separated from the amorphous residue in 40% yield. The long time required for crystallization is due to the low solubility of **1** in CH_2Cl_2. It has so far not been possible, however, to synthesize **1** in more strongly polar solvents.

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1, 92957-32-9; $[(Et)_4N]_2Fe_6S_6I_6$, 88610-35-9; Fe, 7439-89-6; I_2, 7553-56-2.

[1] K. S. Hagen, A. D. Watson, R. H. Holm, *J. Am. Chem. Soc. 105* (1983) 3905, and references cited therein.
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[8] V. K. Shaw, W. J. Brill, *Proc. Natl. Acad. Sci. USA 74* (1977) 3249.
[9] B. K. Burgess, E. I. Stiefel, W. E. Newton, *J. Biol. Chem. 255* (1980) 353.

Structure- and Solvent-Dependence in the Complexation of Lipophilic Substrates in a Water-Soluble Azacyclophane**

By *Hans-Jörg Schneider**, *Klaus Philippi*, and *Jürgen Pöhlmann*

Macrocyclic host molecules with cavities of suitable dimensions can bind lipophilic substrates selectively in aqueous solutions[1]. Monitoring the course of such a complexation by the shifts of NMR signals not only affords information about the encapsulation of the substrate[2] but at the same time also serves as a suitable method for measuring small complexation energies which cannot be determined by, e.g., fluorescence spectroscopic methods[3].

A comparison of the complexation energies of substrates of various sizes and polarity provides important information regarding the dominating non-covalent interactions, e.g. in biological systems. The hitherto rarely investigated influence of solvent- and salt-effects is not only of significance for the mechanism of the complexation, but also for the analytical and catalytic uses of such host compounds[4].

Using the cyclization methods described by *Stetter*[2a,5,9], we have prepared the azacyclophane **1**, which, in contrast

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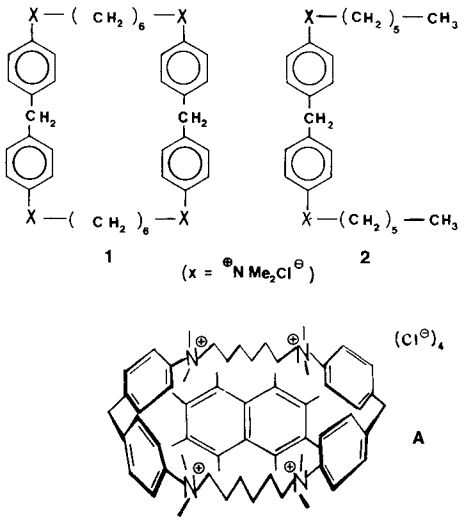
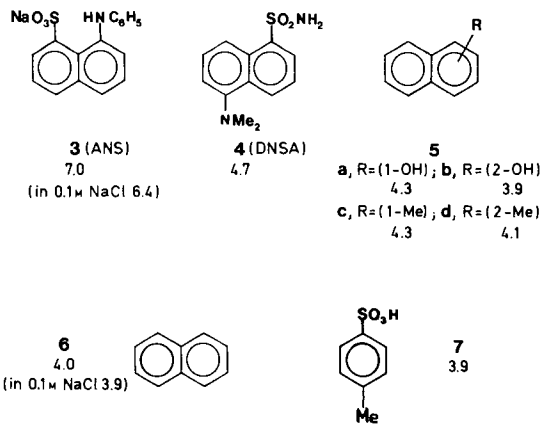
to the analogous host compounds used by *Koga* et al.[2a,b], is, through permethylation, also employable in neutral aqueous solutions and has sufficient methylene groups to accomodate naphthalene derivatives with preservation of a continuous *anti*-conformation of the chain. The shifts of the ^{1}H-NMR resonances of H1 and H2 of $\Delta\delta = -0.91$ and -0.95, respectively, observed in the complexation of naphthalene **6** were analyzed in terms of the anisotropic effects and the significant electric field effects of the ammonium ions. The $\Delta\delta$ values indicate that naphthalene is mainly accomodated equatorially or pseudoaxially (e.g. type **A**); an equilibrium between these forms and small amounts of a conformation with axial orientation cannot be ruled out. Complexations with open-chain host compounds such as **2**, on the other hand, do not lead to any significant shifts in the ^{1}H-NMR resonances.



By NMR spectroscopic monitoring of the reaction of **1** with the guest compounds **4**—**7**, and fluorescence titration of **1** with **3** and **4** in aqueous solutions, we obtained the complexation energies listed in Scheme 1. A numerically simulated curve-fitting was used for the evaluation of binding constants: e.g., the shifts of the ^{1}H-NMR signals of **6** were monitored in water/methanol mixtures (80/20 v/v) between 4×10^{-4}—7×10^{-4} M **6** in the presence of 1.5×10^{-3}—8×10^{-3} M **1**. In the fluorescence titrations the concentrations in water were e.g. 2×10^{-6} mol/L **4** and 0.2×10^{-5}—6×10^{-5} mol/L **1**. The results show that the lipophilic/hydrophobic binding is inadequate in the case of the less voluminous benzene derivatives, whereas in the case of guest molecules having suitable dimensions (**3**—**6**) the complexation energy is increased by about 1/3 by anionic substituents such as in **3**. That compounds without polar substituents are not necessarily more weakly bound (compare **5b** with **5d**, **6**) is consistent with an enhanced hydrophobic effect in the complexation of pure hydrocarbons.

The dominating hydrophobic/lipophilic binding of **3** to **1** is also manifested by the large decrease in complexation energy on increasing the amount of organic solvent. (With predominantly polar bonding the complexation should be stronger in the less polar solvent.) The increase in fluorescence ΔI can serve as a measure of the hydrophobicity (lipophilicity) of a solvent[6]. On plotting the complexation energies ΔG^0 versus the logarithm of the increase in fluorescence ΔI for complexation in water and alcohol mixtures, straight lines are obtained (Fig. 1) whose slopes in the case of the pure hydrocarbon **6** are about twice as



Scheme 1. Complexation energies $\Delta G^0 = RT\ln K$ [kcal/mol] $\pm(0.1-0.2)$ kcal/mol in CH_3OH/H_2O (20/80 v/v) or CD_3OD/D_2O (isotope effect neglected [8]).

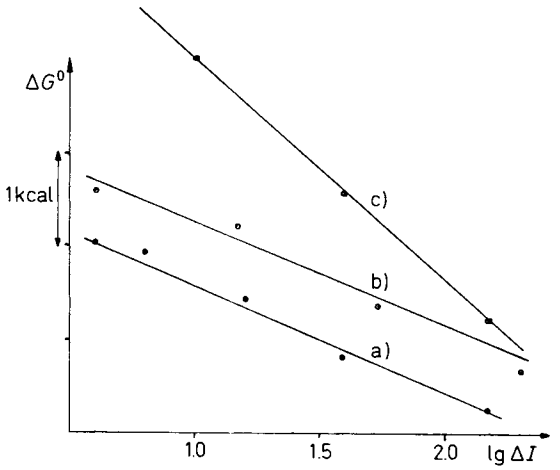


Fig. 1. Free energy of complexation ΔG^0 vs logarithm of the increase in fluorescence $\lg\Delta I$. Solvents: a) **3** + **1** in $MeOH/H_2O$; b) **3** + **1** in $EtOH/H_2O$; c) **6** + **1** in $MeOH/H_2O$.

steep as in the case of **3**. If the transfer energies measured by *Abraham*[7a], e.g. of tetramethyltin from methanol into methanol-water mixtures, are used instead of the ΔI values for the characterization of the hydrophobic properties, a linear correlation ($r = 0.9948$) likewise results with a slope $m = 0.46$ (cf. plot of ΔG^0_{cplx} of **3**). These results underscore the comparable mechanism in the binding of hydrophobic substrates in lipophilic cavities. The substantial decrease in complexation energy observed in some cases upon addition of salts (see Scheme 1) is strongly pronounced in the case of substrates with highly polar substituents, due to electrostatic interactions.

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German version: *Angew. Chem.* 96 (1984) 907

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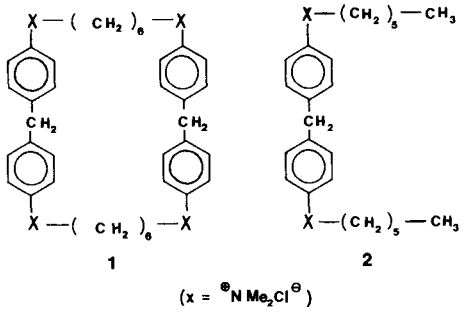
Thin Layer Chromatography with an Immobilized Azacyclophane Derivative as Analytical Agent and Probe for Host-Guest Interactions**

By *Hans-Jörg Schneider**, *Walter Müller*, and *Detlev Güttes*

Dedicated to Professor Egon Stahl on the occasion of his 60th birthday

Macrocyclic compounds enable chromatographic separations of guest molecules by selective inclusion, as demonstrated hitherto mainly with ions[1]. We have found that easily handleable chromatographic techniques are accessible by immobilization of the azacyclophane **1** on silica gel layers. As a rule, the azacyclophane derivative does not hinder detection by fluorescence under the UV lamp or by customary developing reagents[2]. On application of the dissolved substances the starting spots are usually less spread out than on untreated layers. We hoped, by means of this technique, also to obtain information about the nature of host-guest interactions.



Experiments with aromatic guest molecules, inter alia with azo dyes, show that only compounds with acidic groups, particularly groups such as $R=SO_3H$, are selectively bound. Hereby, we define the selectivity S by the percent decrease in R_f obtained with **1**.

$$S\,[\%] = (1 - R_f/R_{fo}) \times 100$$

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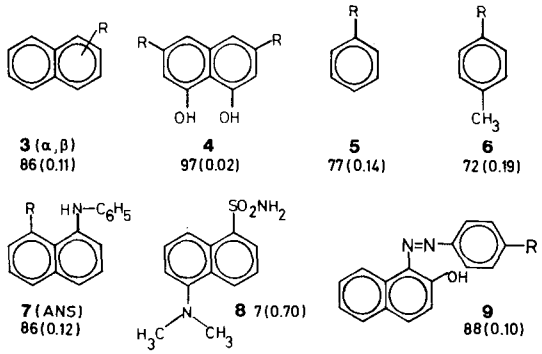
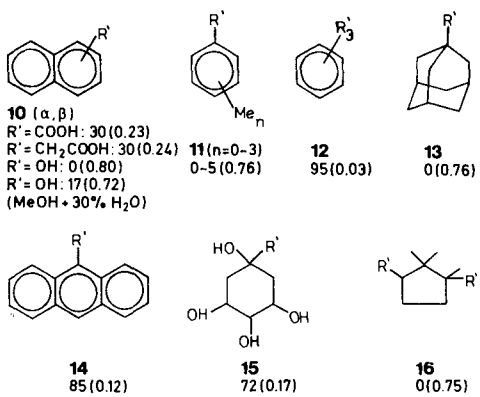
S can reach up to approximately 100%. The S values and, in brackets, R_f values observed for the complexation of **3**—**25** on the chromatographic plates loaded with **1** are given in Schemes 1, 2, and 3.



Scheme 1. $R=SO_3H$, methanol as eluent; error in S: ±4%.

Besides the acidity of the substituents, the geometry of the hydrocarbon framework also has a decisive influence on the selectivity (cf. **5**, **6**); this is consistent with the order of lipophilicity and complexation observed, inter alia, in solution by NMR spectroscopy[3]. For the selective binding of different substrates, a most effective inclusion as possible in the cavity of immobilized **1** is essential. This follows from the generally far higher selectivities of naphthyl derivatives compared to the corresponding phenyl derivatives as well as from the considerably lower selectivities which are found with the immobilized open-chain analogue **2**: Here the S values obtained with sulfonic acids are only 20—40% instead of an average of 88%.

Carboxylic acids are still complexed selectively if the lipophilic residue fits in the cavity of **1** (Scheme 2, compare **10** with **11** and **13**) or if the electrostatic attraction can be realized by several substituents (cf. **12**, **15**). Phenolic groups are not acidic enough to lead to selectivity in methanol. On the other hand, the addition of water in this case leads, as also in solution[1], to a strengthening of the binding (cf. **10**, Scheme 2).



Scheme 2. R'=COOH, methanol as eluent; error in S: ±(4—8%).

A simple strategy for increasing the selectivity in the case of substrates with weakly dissociating groups consists in the use of an alkaline solvent, which enables novel separations to be realized, also in the case of natural products (Scheme 3). In the case of amino acids and peptides, protecting groups on the nitrogen which reduce the betaine participation and enhance the lipophilicity usually effect an increase in the selectivity.

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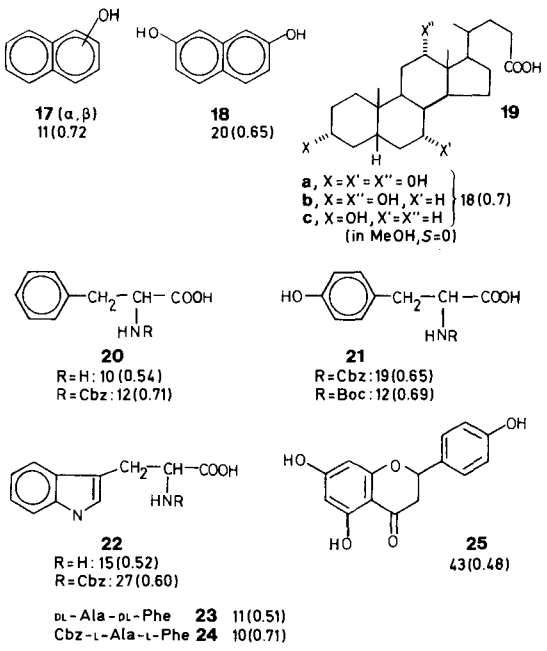

Scheme 3. Methanol with 2% conc. NH_3-solution as eluent; error in S: ±4%; Cbz = benzoyloxycarbonyl, Boc = *tert*-butoxycarbonyl.

According to the selectivities measured here and the findings of spectroscopic investigations in solution[3], the vital factors of the complexation are the lipophilic/hydrophobic binding in the cavity of the macrocycle and the electrostatic attraction between polar substituents in the substrate and the positive charges in the host molecule. The participation of electrostatic attraction should increase in a solvent less polar than water (e.g. methanol)[3], and dominates in the binding to the immobilized macrocycle. This is consistent with the hypothesis that conformational perturbations by the immobilization very strongly affect the dispersive participation of lipophilic interactions, whereas coulomb attractions are notably less geometry-dependent.

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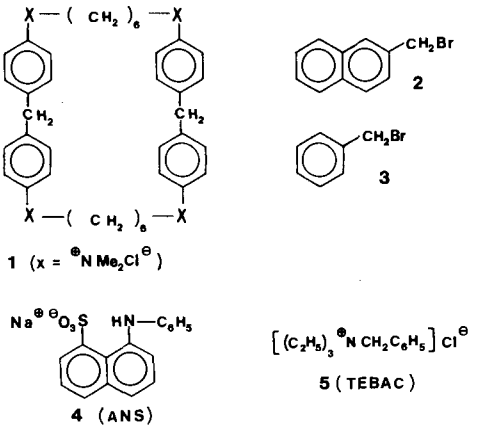
An Azacyclophane Derivative as Catalyst of Substrate- and Product-Selective Reactions with Ambident Anions**

By *Hans-Jörg Schneider** and *Rainer Busch*

The utilization of macrocyclic host compounds as selective catalysts and as enzyme models represents one of the major breakthroughs in organic chemistry[1]. Crown ethers have often been employed for the acceleration of nucleophilic exchange reactions, but mainly as unspecific phase-transfer catalysts[2]. Although cases of a selective complexation of the anion and concomitant enhancement of reactivity are known[3], to our knowledge there are no examples of such reactions with enzyme-like selective substrate binding. After having demonstrated, both spectroscopically as well as by thin-layer chromatography, that naphthalene derivatives are inserted selectively into the relatively easily accessible macrocycle **1**[1a,b], we have investigated the use of **1** in nucleophilic exchange reactions.



Reaction of 2-bromomethylnaphthalene **2** with an excess of sodium nitrite (for concentrations, see Table 1) is accelerated in the presence of **1**, e.g. in a 0.4 M solution of **1** by a factor of 20; concomitantly, the product ratio [R–ONO]:[R–NO_2] obtained with the ambident nucleophile changes from 0.50:1 to 0.16:1 (Fig. 1). However, since **1** is an ammonium salt, the product ratio must be compared with that which is obtained in the presence of Me_4NCl. Considering it this way, the product ratio changes by a factor of about 50 (Table 1). The phase-transfer catalyst benzyltriethylammonium chloride **5** also steers the product pattern in the opposite sense to **1** and without any increase in the reaction rate, thus proving the absence of unspecific effects or micelle effects. Using the pseudo-first order rate constants obtained at the initial stage of the reaction in combination with a numerical curve-fitting, the stability constants of the complex and the rate constants of

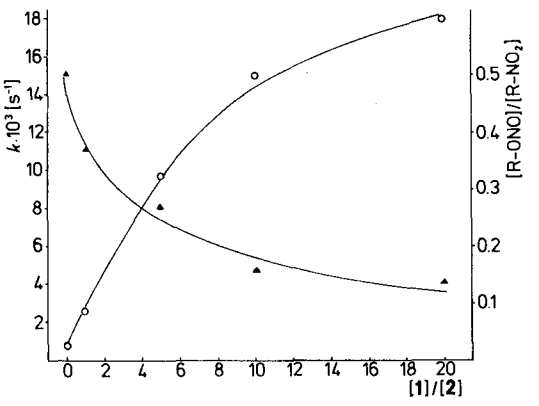


Fig. 1. Experimental rate constants of the catalyzed reaction; o–o–o–o–, left-hand scale; product ratio [R–ONO]/[R–NO_2] as a function of the ratio [catalyst]/[substrate]; ▲–▲–▲–, right-hand scale.

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Table 1. Examples of the kinetics and product ratios [a].

Nu	Substrate	Additive	$k \times 10^3$ [b]	Product ratio	
				[R–ONO]	: [R–NO_2]
$NaNO_2$	**2**	—	0.7	0.50	: 1
$NaNO_2$	**2**	**1**	2.6	0.37	: 1
$NaNO_2$	**2**	**1** + **4**	0.6	0.53	: 1
$NaNO_2$	**2**	**5**	1.1	20	: 1
$NaNO_2$	**2**	$^{\oplus}NMe_4Cl^{\ominus}$	—	6.7	: 1
$NaNO_2$	**3**	—	1.2	0.34	: 1
$NaNO_2$	**3**	**1**	1.2	0.32	: 1
				[R–NC]	: [R–CN]
NaCN	**2**	—	0.9	<0.010	: 1
NaCN	**2**	**1**	3.4	<0.010	: 1
NaCN	**2**	**5**	1.1	<0.010	: 1
				[R–NCS]	: [R–SCN]
NaSCN	**2**	—	8.6	<0.010	: 1
NaSCN	**2**	**1**	17	<0.010	: 1

[a] In dioxane/water (1 : 1) at 30 °C. Conditions: nucleophile [Nu] 0.43 M; substrate [**2**] or [**3**] as well as catalyst [**1**] and inhibitor [**4**] 0.043 M in each case; [**5**] 0.43 M; [Me_4NCl] 0.43 M. [b] Rate constant k pseudo-first order [s^{-1}] ± 10%. Kinetics and product compositions analyzed ^{1}H-NMR spectroscopically.

the ensuing reaction (Fig. 1) can be estimated as being ca. $K_a = 4.1$ L/mol and $k_c = 2.1 \times 10^{-2}\ s^{-1}$, respectively[4]. This leads to a value of $k_c/k_o \approx 30$ as a measure of the effectiveness of **1** ("effective concentration"[5]) under the conditions mentioned in Table 1. Both the observed acceleration of the reaction as well as the product control can be interpreted in terms of a "proximity effect"[5] or in terms of an accumulation of nitrite ions at the positively charged centers of **1** in the complex. This leads to an increase in the proportion of S_N2-reaction and thus to increased attack at the nitrogen atom instead of the oxygen atom of the ambident anion.

In the case of $CN^{\ominus}$ and $SCN^{\ominus}$ ions the attack at the carbon or sulfur atom, respectively, predominates to such an extent[6] that **1** no longer effects a change in the product ratio, though a marked increase in the rate of reaction is still observed (Table 1).

On addition of the fluorescence indicator **4**, which binds very strongly to the macrocycle **1**[1a,b], the catalyst becomes inhibited; this also manifests itself in an unchanged product ratio (Table 1).

In contrast to the naphthyl derivative **2**, benzyl bromide **3** leads neither to a change in the product ratio nor to an increase in the reaction rate, since phenyl derivatives are far more weakly bound in the cavity of **1**[1a,b]. This is confirmed by the energies of complexation of **2** and **3** with **1** obtained by NMR spectroscopic measurements (**2**: $K_{ass} = 25$, **3**: $K_{ass} = 3.5$ L/mol, measured in dioxane/water (1 : 1) without added salt). The shifts of the ^{1}H-NMR resonances observed only in the complexation of **2** with **1** indicate the formation of the inclusion complex responsible for the catalysis.

The system presented here combines many features typical for an enzyme: Increase in reaction rate, saturation kinetics, substrate specificity, selective control of reaction, competitive inhibition.

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[4] K_a and k_c for the basic reactions

$$\mathbf{1} + \mathbf{2} \overset{K_a}{\rightleftharpoons} \mathbf{C}\,(\text{complex})$$

$$\mathbf{2} + \text{Nu} \xrightarrow{k_o} \mathbf{P}\,(\text{product})$$

$$\mathbf{C} + \text{Nu} \xrightarrow{k_c} \mathbf{P}$$

were varied with a computer program (R. Kramer, unpublished) under the condition [Nu] = const. (excess of Nu, see Table 1) until the numerical integration of the differential equations as well as the measured time-conversion values (linearization according to pseudo-first order possible, $\triangleq k_{exp}$) correctly reproduced the dependence of the k_{exp} values on the ratio [**1**]/[**2**] (see Fig. 1).

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Isocyanide Insertion into a Uranium-Carbon Double Bond**

By *Roger E. Cramer**, *K. Panchanatheswaran*, and *John W. Gilje**

Carbon monoxide is known to insert into actinoid-carbon double[1] and single bonds[2,3]. However, the chemically similar, but often more reactive, isocyanides have not been reported[3] to undergo similar reactions.

We have previously reported[4] that acetonitrile reacts at the uranium-carbon multiple bond[5,6] of **3** to produce an imido complex containing a U–N bond with approximately triple-bond character. In related hydrido(organo)-yttrium chemistry, *tert*-butyl isocyanide inserts into the Y–H bond of **1** to afford **2**[7]. The same yttrium hydride reacts with nitriles to produce dimeric complexes containing bridging alkylideneamido ligands[8].

$$\underset{\mathbf{1}}{[Cp_2YH(THF)]_2} + CN\mathit{t}Bu \longrightarrow \underset{\mathbf{2}}{[Cp_2Y(\eta^1 : \eta^2\text{-}HC{=}N\mathit{t}Bu)]_2}$$

$$\underset{\mathbf{3}}{Cp_3U{=}CHPPh_2Me} + CNC_6H_{11} \longrightarrow \underset{\mathbf{4}}{Cp_3U\begin{matrix}\diagup N{-}C_6H_{11} \\ \diagdown C{=}CH{-}PPh_2Me\end{matrix}}$$

Scheme 1. Cp = η^5-C_5H_5, thf = tetrahydrofuran.

In view of the affinity of U^{IV} for hard Lewis bases, the known carbon monoxide chemistry, and related yttrium chemistry, we investigated the reaction between **3** and cyclohexyl isocyanide. In this reaction $C_6H_{11}NC$ inserts into the UC double bond in **3** forming a unique uranaazacyclopropene **4** in which both nitrogen and carbon atoms are

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tightly bonded to uranium. In contrast to metal-carbon single bonds, where CC single bonds form during insertion reactions, insertion at the U=C double bond leads to a new *unsaturated* ligand.

The reaction of **3** and $C_6H_{11}NC$ (molar ratio 1 : 1, 1 h) in ether produces a red solution from which **4** can be isolated as red crystals in 53% yield after evaporation of the solvent followed by recrystallization from a 1 : 1 benzene-pentane mixture. The ^{1}H-NMR spectrum shows paramagnetically shifted peaks [7], and the IR spectrum is complex, but does not exhibit a peak at ca. 2136 cm^{-1}, a characteristic frequency for $C_6H_{11}NC$[10].

4 can be stored for months in vacuo or under anhydrous nitrogen, but decomposes within seconds if exposed to the atmosphere. It is very soluble in aromatic solvents and ethers, but only slightly soluble in aliphatic hydrocarbons.

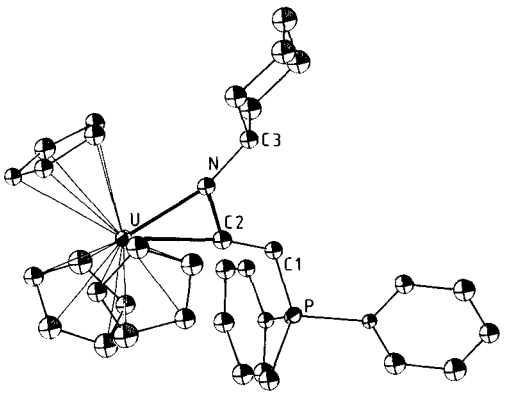

Fig. 1. ORTEP representation of **4**. Angles [°]: U-N-C2 78(1), U-C2-N 68(1), N-C2-C1 122(2), C2-N-C3 120(2), P-C1-C2 124(2), N-U-C2 33.8(9), U-N-C3 161(2). For distances, see text.

The X-ray crystal structure of **4**[11] (Fig. 1) shows that the molecule contains three Cp rings and an η^2-$CN(C_6H_{11})CHPh_2Me$ ligand. The UN distance (2.31(2) Å) is not statistically different from that in Cp_3UNPh_2 (2.29(1) Å), where the UN bond order is between 1 and 2[12], and the UC2 distance (2.44(3) Å) can be compared to the UC single bond distance in $Cp_3UC_4H_9$ (2.43(2) Å)[13]. The distance C1C2 (1.33(3) Å) is typical of a CC double bond, the distance PC1 (1.74(2) Å) is not significantly shorter than that of P–C single bonds in phosphonium ions, and the distance N-C2 (1.39(4) Å) is not statistically different from that of a normal single bond. In contrast, the length of the CN double bond in **2** is 1.275(6) Å[7]. The best description of the bonding is shown in Scheme 1.

Organoactinoid complexes tend to be sterically shielded, but electronically unsaturated[4]. The formation of **4** demonstrates the tendency of U^{IV} to partially relieve its electron deficiency by interaction with multielectron donor ligands.

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3, 77357-86-9; **4**, 92937-92-3; CNC_6H_{11}, 931-53-3; C, 7440-44-0; U, 7440-61-1.

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[9] ^{1}H-NMR (300 MHz, C_6D_6, 25 °C): $\delta = -13.77$ (15H, s, Cp_3U); 73.13 (1H, d, J (PCH) = 27 Hz, HCP); 23.78 (3H, d, J (PCH) = 9 Hz, MeP); 15.75, 9.16, 8.67 (4H, 4H and 2H, each m, PhP); 0.66 (2H, d, $J = 4$ Hz); 0.50 (1H, d, $J = 2.5$ Hz); 0.16 (2H, d, $J = 4$ Hz); -1.18 (1H, d, $J = 4$ Hz); -5.38 (2H, d, $J = 4$ Hz); -7.68 (2H, br); -11.75 (1H, s), all C_6H_{11}.
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Di-(μ-amido)dirhodium Complexes: Structure of $[Rh_2(\mu\text{-}(NH)_2naphth)I_2(CO)_2(PPh_3)_2]$

By *Luis A. Oro**, *Maria J. Fernández, Javier Modrego, Concha Foces-Foces,* and *Felix H. Cano*

Dinuclear transition-metal complexes and their reactions have been the subject of considerable interest in recent years[1]. As part of our studies exploring the use of nitrogen donor ligands for the construction of di- or multinuclear rhodium complexes[2], we describe a facile route to di(μ-amido)dirhodium complexes. Amido-bridged compounds are relatively rare[3], and to the best of our knowledge no related di(μ-amido)-bridged metal complexes have been described.

We report here on the synthesis of a novel family of dinuclear amido complexes containing deprotonated 1,8-diaminonaphthalene $[(NH)_2naphth]^{2\ominus}$ as a bisdihapto-bridging ligand. The isolated complexes **1**—**3**[4] were prepared as outlined in Scheme 1[5].

$$2\ Rh(acac)(CO)_2 \xrightarrow[-\ 2\ acacH]{+\ (NH_2)_2naphth} \underset{\mathbf{1}}{Rh_2(\mu\text{-}(NH)_2naphth)(CO)_4} \xrightarrow[-\ 2\ CO]{+\ 2\ PPh_3} \underset{\mathbf{2}}{Rh_2(\mu\text{-}(NH)_2naphth)(CO)_2(PPh_3)_2} \xrightarrow{+\ I_2} \underset{\mathbf{3}}{Rh_2(\mu\text{-}(NH)_2naphth)I_2(CO)_2(PPh_3)_2}$$

Scheme 1.

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Complex **1** exhibits C_{2v} symmetry, and complexes **2** and **3** each show one broad ν(CO) band; the observed shift of the ν(CO) band ($\Delta\nu$(CO) = 70 cm^{-1}) is consistent with a two-center oxidative addition of I_2 to both Rh centers with concurrent formation of an Rh–Rh bond[4].

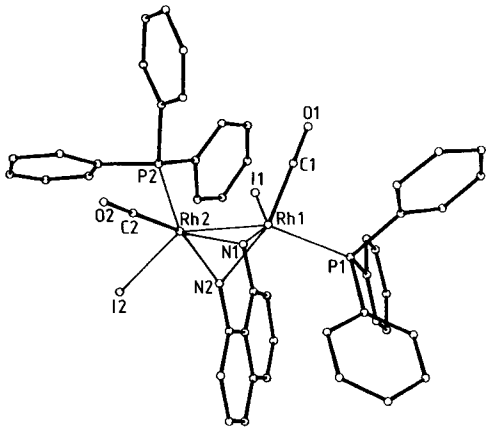

Fig. 1. Structure of $3 \cdot 1/2\,CH_2Cl_2$ in the crystal. Selected bond distances [Å] and torsion angles [°]: Rh1-C1 1.831(23), Rh1-I1 2.692(2), Rh1-P1 2.374(4), Rh2-C2 1.806(17), Rh2-I2 2.742(1), Rh2-P2 2.307(4) and I1-Rh1-Rh2-I2 −127.1(1); cf. also text.

The structure of complex **3** has been confirmed by single-crystal, X-ray analysis[6] and appears to be the first example wherein a rhodium-rhodium bond is bridged by a di(μ-amido) ligand (Fig. 1). The dinuclear molecule has no crystallographic symmetry. The molecule would exhibit a mirror plane through the di(μ-amido) ligand if the sets of P, C, I ligands were mutually twisted through −120°. Interesting features of the structure are the short distance between the Rh atoms (2.540(1) Å) and the low value of the RhN-Rh angles (75.5(4) and 74.5(4)°). The Rh-N bond lengths (2.078(12), 2.072(10), 2.081(12) and 2.117(12) Å) are similar to those found in some related amido-bridged platinum(II) complexes[3].

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CAS Registry numbers:
1, 92900-70-4; **2**, 92900-71-5; $3 \cdot ½\ CH_2Cl_2$, 92900-73-7; $Rh(acac)(CO)_2$, 14874-82-9; I_2, 7553-56-2; Rh, 7440-16-6.

[1] See e.g. Proceedings of the EUCHEM Conference, The Challenge of Polynuclear Inorganic Compounds, *Inorg. Chim. Acta 1982*, 62.

[2] L. A. Oro, M. A. Ciriano, B. E. Villarroya, A. Tiripicchio, F. J. Lahoz, *J. Chem. Soc. Chem. Commun. 1984*, 521.

[3] M. K. Cooper, P. V. Stevens, M. McPartlin, *J. Chem. Soc. Dalton Trans. 1983*, 553.

[4] **1**: A solution of $Rh(acac)(CO)_2$ (200 mg, 0.77 mmol) and 1,8-$(NH_2)_2$naphth (203 mg, 0.77 mmol) in CH_2Cl_2 is stirred for 0.5 h at room temperature. After concentration of the solution, addition of diethyl ether yields yellow crystals, which are filtered off, washed with diethyl ether, and air dried. Yield: 135 mg (74%); IR ν(CO)(CH_2Cl_2): 2070, 2050 and 1995 cm^{-1}.—**2**: A solution of **1** (125 mg, 0.26 mmol) in CH_2Cl_2 is allowed to react with PPh_3 (138 mg, 0.52 mmol) for 0.5 h at room temperature. Addition of diethyl ether produces yellow crystals, which are filtered off, washed with diethyl ether, and air dried. Yield: 186 mg (75%); IR ν(CO) (CH_2Cl_2): 1950 cm^{-1}.—**3**: A solution of **2** (180 mg, 0.19 mmol) in CH_2Cl_2 is treated with I_2 (48 mg, 0.19 mmol) for 0.5 h at room temperature. Addition of diethyl ether yields violet crystals, which are filtered off, washed with diethyl ether, and air dried. Yield 182 mg (80%); IR ν(CO) (CH_2Cl_2): 2020 cm^{-1}.—All compounds gave satisfactory microanalytical data (C, H, N) and molecular weight measurements.

[5] This synthetic strategy may have wider implications for the preparation of dinuclear metal complexes.

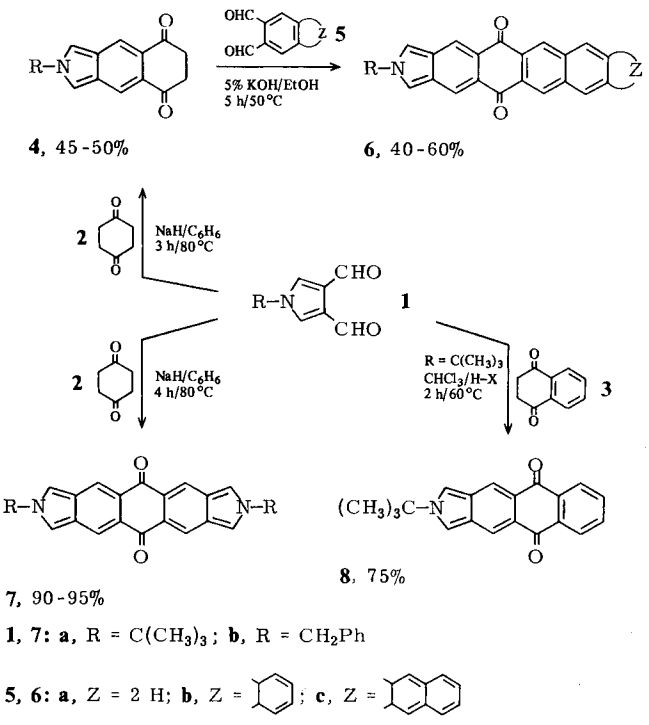
[6] Crystal structure analysis of $3 \cdot 1/2\,CH_2Cl_2$. P1, $a = 18.3812(29)$, $b = 13.2529(18)$, $c = 10.4947(13)$ Å, $\alpha = 102.861(11)$, $\beta = 100.996(12)$, $\gamma = 71.065(12)°$, $V = 2339.1(5)$ $Å^3$, $\rho_{calc.} = 1.759$ $g \cdot cm^{-3}$, $Z = 2$, $\mu(Cu_{K\alpha}) = 179.18$ cm^{-1}. 7873 independent reflections, Philips PW1100 diffractometer with $2\theta < 65°$. Patterson methods. Refinement was carried out on F_0 values with three block matrix and anisotropic thermal model for the non-H atoms. The H atoms were kept isotropic. R factor = 0.074 for the 4632 observed reflections ($F_0 > 4.5\sigma(F_0)$).—Further details of the crystal structure analysis are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.

Oligocyclic Hetarenes with Quinonoid Structure; Synthesis by Sequential Cyclizing Condensation**

By *Richard P. Kreher** and *Jürgen Pfister*

Due to the *o*-quinonoid structure[1], the synthesis of annelated 2*H*-isoindoles is very exacting. For the rational preparation of oligocyclic hetarenes **6**, **7** and **8**, practicable, universally applicable synthetic steps are required. According to our findings the cyclizing condensation[2] of hetero- and carbocyclic dicarbaldehydes **1** and **5**, respectively, with 1,2-bifunctional CH-acidic dicarbonyl compounds **2**, **3**, or **4** fulfills these requirements.

A general method has been developed for the preparation of the requisite 1-alkyl-1*H*-pyrrole-3,4-dicarbaldehydes **1** from the readily accessible *N*-alkyl-*N*-formylglycines[3–5].



1, 7: a, R = $C(CH_3)_3$; **b**, R = CH_2Ph

5, 6: a, Z = 2 H; **b**, Z = ; **c**, Z =

1a and **1b** are condensable with 1,4-cyclohexanedione **2**[6] if sodium hydride in anhydrous benzene is used for the deprotonation and induction of the twofold elimination of water. Reaction of equimolar amounts of **1** and dione leads to formation of the isolable primary condensation

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[**] Structure and Reactivity of Isoannelated Heterocyclic Systems with $4n\pi$- and $(4n+2)\pi$-Electrons, Part 11. This work was supported by the Fonds der Chemischen Industrie.—Part 10: R. Kreher, K. Mildenberger, *Chem.-Ztg. 108* (1984) 317.

products **4**, which according to the spectroscopic findings are present in the carbonyl form [ν(CO) = 1680 cm^{-1}]; in trifluoroacetic acid the tautomeric hydroxy form of the condensation product is formed.

Due to the carbonyl structure, the tricycles **4** are ideal components for the synthesis of oligocyclic (4n + 2)π-systems with *o*- and *p*-quinonoid structure. We have now found that further sequential condensation with **1** affords access to the 2*H*-isoindoles **7**, which are fused via carbonyl groups in the 5,6-position [ν(CO) = 1660 cm^{-1}]; these symmetric pentacyclic hetarenes can be prepared in one step from the educts **1** and **2** in the molar ratio 2 : 1. The alternative condensation of **4** with the carbocyclic 1,2-dicarbaldehydes **5a—c** opens up an entry to the oligocyclic hetarenes **6a—c** [ν(CO) = 1670 cm^{-1}]. The synthesis of these topologically interesting N-heterocycles by the methods commonly used so far[1] would be too tedious and expensive.

1,4-Naphthalenediol, which, in the carbonyl form **3**, reacts as a 1,2-bifunctional CH-acidic component, can be used instead of **2**. Cyclizing condensation of **3** with **1a** provides a rational access to the tetracyclic hetarene **8** [ν(CO) = 1650 and 1660 cm^{-1}][7].

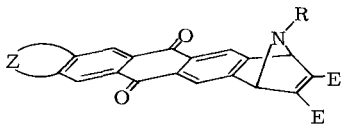
The ochre to red colored oligocyclic hetarenes **6a—c** [λ_{max}(CHCl$_3$) = 415—525 nm] and **8** [λ_{max}(CHCl$_3$) = 465 nm] are soluble in trifluoroacetic acid and concentrated sulfuric acid; the colors of these solutions are different (green to violet) and are presumably determined by solvation and association. The extremely high melting points of **6** (m.p. > 350°C), **7** (m.p. > 350°C) and **8** (m.p. = 264—265°C) demonstrate the astonishingly high thermal stability of these compounds and are indicative of association in the solid state. The IR bands for the carbonyl groups [ν(CO) = 1650—1670 cm^{-1}] differ very little from those of the structurally similar acenoquinones[8] [ν(CO) = 1670—1675 cm^{-1}].

In the ^{1}H-NMR spectra ($CDCl_3$) the chemical shifts for 1-H and 3-H (δ = 7.58—7.66) in the position adjacent to nitrogen are dependent upon the degree of annelation; the deshielding effect of the acene system gives rise to a downfield shift. According to the ^{1}H-NMR spectra in trifluoroacetic acid, **6** and **8** are protonated exclusively at the position adjacent to the nitrogen; no evidence has been found for a protonation of the carbonyl groups. Hence, the vinylogous acid amide structure has no influence on the reactivity of the oligocyclic hetarenes **6** and **8**. In the case of the pentacyclic benzo[1,2-*f*;4,5-*f*']diisoindoles **7** a protonation of the two terminal pyrrole rings is detectable.

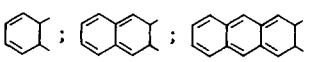
Despite multiple annelation, the characteristic properties of 2*H*-isoindoles[1] are preserved: **6** and **8** react with dimethyl acetylenedicarboxylate at room temperature; cycloaddition at the 1,3 position leads to formation of crystalline 1 : 1 adducts **9**. In the case of **7**, twofold cycloaddition affords 1,2-adducts **10** with *syn*- and *anti*-configuration.

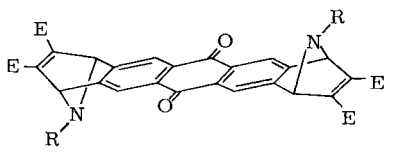
The reactivity and regioselectivity towards dienophiles is accordingly not changed by the linear annelation; regiospecific reactions of the *peri*-positions are not detectable—even in the case of the heptacyclic hetarene **6c**. In this respect there are marked differences to the π-isoelectronic acenes[9].

The oligocyclic hetarenes[10] **6**, **7**, and **8** are of interest to us as colored redox systems and as precursors for the reduction to 2*H*-aceno[2,3-*f*]isoindoles.



9, E = $COOCH_3$

Z = 2 H; 



anti-**10**, E = $COOCH_3$

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1a, 92763-71-8; **1b**, 92763-72-9; **2**, 637-88-7; **4a**, 92763-73-0; **4a** (hydroxy form), 92763-75-2; **4b**, 92763-74-1; **4b** (hydroxy form), 92763-76-3; **5a**, 643-79-8; **5b**, 7149-49-7; **5c**, 76197-35-8; **6a** (R = C(CH$_3$)$_3$), 92763-79-6; **6b** (R = C(CH$_3$)$_3$), 92763-80-9; **6c** (R = C(CH$_3$)$_3$), 92763-81-0; **7a**, 92763-77-4; **7b**, 92763-78-5; **8**, 92763-82-1; **9a** (R = C(CH$_3$)$_3$), 92763-83-2; **9b** (R = C(CH$_3$)$_3$), 92763-84-3; **9c** (R = C(CH$_3$)$_3$), 92763-85-4; **9** (Z = 2,3-anthryl, R = C(CH$_3$)$_3$), 92763-86-5; *anti*-**10** (R = C(CH$_3$)$_3$), 92763-81-6; *syn*-**10** (R = C(CH$_3$)$_3$), 92843-01-1; *N*-*tert*-butyl-*N*-formylglycine, 90544-83-5; *N*-benzyl-*N*-formylglycine, 86731-89-7; dimethyl 1-*tert*-butyl-1*H*-pyrrole-3,4-dicarboxylate, 74986-19-9; dimethyl 1-benzyl-1*H*-pyrrole-3,4-dicarboxylate, 78394-12-4; 1-*tert*-butyl-3,4-dihydroxymethyl-1*H*-pyrrole, 92763-88-7; 1-benzyl-3,4-dihydroxymethyl-1*H*-pyrrole, 92763-89-8; 1,4-naphthalenediol, 571-60-8; dimethyl acetylendicarboxylate, 762-43-5.

[1] Review: a) R. T. Brown, J. A. Joule, P. G. Sammes in D. Barton, W. D. Ollis, P. G. Sammes: *Comprehensive Organic Chemistry, Vol. 4*, Pergamon Press, Oxford 1979, p. 477; b) R. Bonnett, S. A. North, *Adv. Heterocycl. Chem. 29* (1981) 341.

[2] The cyclizing condensation of 1*H*-pyrrole-3,4-dicarbaldehydes with 1,3-bifunctional compounds containing CH-acidic groups is a convenient synthetic principle for the annelation of seven-membered carbocycles and heterocycles; R. Kreher, H. Hennige, H. Möller, *Allg. Prakt. Chem. 23* (1972) 82; R. Kreher, G. Vogt, *Angew. Chem. 82* (1970) 958; *Angew. Chem. Int. Ed. Engl. 9* (1970) 955; R. Kreher, G. Vogt, M.-L. Schultz, *ibid. 87* (1975) 840 and *14* (1975) 821; R. Kreher, H. Möller, P. H. Wagner, *ibid. 88* (1976) 419 and *15* (1976) 382.

[3] J. Pfister, Diplomarbeit, Technische Hochschule Darmstadt 1982; part of a Dissertation, Universität Dortmund.—*N*-Alkyl-*N*-formylglycines were allowed to react with dimethyl acetylenedicarboxylate in the presence of acetic anhydride. The cyclization to the 1,3-oxazolium 5-oxide [4] was followed by dipolar cyclization with the active alkyne and cleavage of the CO_2. The dimethyl 1-alkyl-1*H*-pyrrole-3,4-dicarboxylates were reduced with $LiAlH_4$; the hydroxymethyl compounds thus obtained were chemoselectively oxidized with barium manganate [5].

[4] Review: C. G. Newton, C. A. Ramsden, *Tetrahedron 38* (1982) 2965.

[5] H. Firouzabadi, E. Ghaderi, *Tetrahedron Lett. 1978*, 839.

[6] a) Cyclization of 2,3-naphthalenedicarbaldehyde **5b** with 1,4-cyclohexanedione **2**: W. Ried, F. Anthöfer, *Angew. Chem. 66* (1954) 604; *ibid. 65* (1953) 601; cyclization of substituted 3,4-furan- and 3,4-thiophenedicarbaldehydes: L. Lepage, Y. Lepage, *Synthesis 1982*, 882.

[7] The synthetic principle of cyclizing condensation is flexible: As heterocyclic dicarbaldehydes, 1*H*-pyrazole-3,4- and 2*H*-1,2,3-triazole-4,5-dicarbaldehydes are just as capable of cyclizing as are dialkyl acetonedicarboxylates as 1,3-bifunctional carbonyl compounds [3].

[8] A. Verine, Y. Lepage, *Bull. Soc. Chim. Fr. 1973*, 1154.

[9] D. Biermann, W. Schmidt, *J. Am. Chem. Soc. 102* (1980) 3163, 3173, and references cited therein.

[10] The new compounds were unequivocally characterized by elemental analysis as well as by ^{1}H-NMR, IR, and mass spectra.

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Carbanion Chemistry. By *R. B. Bates* and *C. A. Ogle*. Springer-Verlag, Berlin 1983. vii, 117 pp., bound, DM 48.00.

The title and size of this work raise hopes of an introduction to carbanion chemistry; there is an unfilled need here, since the most recent introduction is already ten years old.

However, the foreword reveals that the authors' aspirations are much lower: "This book was prepared with the idea of collecting together some of the multitudinous new literature on carbanions and presenting it along with the fundamentals of carbanion chemistry". Furthermore, an emphasis is promised on results published in the years 1976—1982 with about half of the 785 references.

Eight chapters (74 pp.) deal with the structure, synthesis and reactions of carbanions and organoalkali metal, alkaline earth, aluminium, zinc and cadmium compounds in an exceedingly compressed form. Chapter IX (2 pp.) "Carbanion Equivalents" might well have been omitted without incurring any loss of relevant information; the compilation of (very arbitrarily) chosen synthetic equivalents for not directly accessible carbanions, without commentary, is scarcely helpful. The alternative—a detailed inclusion of preparative applications—would fall outside the framework of this little book.

The number of topics covered in such a small space means that problems can only be touched upon and deeper insights cannot be conveyed. Attempts to extract principles are only occasionally made and even then seem mostly superficial. Thus, concerning the regioselectivity of electrophilic substitution of dianions (a field in which *Bates* is involved) we are only presented with the following rule of thumb (p. 42): "... the first reaction with an electrophile will occur where the last proton came off (assuming the dianion was generated by removal of protons)". Apart from the fact that there are many exceptions to the rule (amongst other reasons because several CH acids can act as precursors for the same dianion), the reader is given no aid in further understanding.

Recent developments, such as dominate the carbanion literature today and which were already in full progress in 1981 (e.g. the stereoselective substitution of carbanions, the change of selectivity by metal exchange, and lithiations directed by heteroatoms), can be recognized by the insider but they merge in the uniformity of the material.

Did the authors just wish to offer assistance in the rapid tracing of original publications? If so there are some minus points to be awarded here. First, they do not fulfill completely the promise they give in the foreword, since only five publications are cited from 1982 (of which three are the authors' own). Furthermore, the reviewer was not able to discover what the criteria were for selecting the literature. Which of the publications are the most important is usually controversial. Apart from this, the literature from German-speaking areas seems to be greatly underrepresented. Only a few groups from this sector may find their contributions adequately represented. The number of references (from a total of 785) is a rough and ready but telling measure: *Seebach* (21), *Schlosser* (6), *Schöllkopf* (5), *Kauffmann* (4), *Hünig* (2), *Bestmann* (1), *R. R. Schmidt* (1), *Reetz* (1), etc. Basic publications also remain unmentioned. For example, there is no mention of the extremely useful allopolarization principle (*Gompper*, review 1976) or of *Boche*'s publications concerning the torsion dynamics of allyl anions; the list could be extended. It is also troublesome that reviews are not labeled and that there is no author index.

The numbers of mistakes and printing errors have been held down to acceptable levels. In spite of the inadequacies discussed this book can be recommended to all who are concerned with carbanions, because everyone will find topics of interest to him amongst the abundance. The newcomer, however, is recommended for introduction, the exciting reading of "Schlosser" (published by the same company in 1973)—Struktur und Reaktivität polarer Organometalle—as a preliminary.

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Dynamic NMR Spectroscopy. By *J. Sandström*. Academic Press, London 1982. x, 226 pp., bound, $ 39.50.

This book is neither a new edition nor a substitute for the standard work of the same name published by *Jackman* and *Cotton* in 1975. Those expecting a survey of the most important new DNMR investigations will be disappointed. To be sure almost all the techniques (with the exception of 2 D experiments) are mentioned and typical areas of application presented using examples (ligand permutations of transition metal complexes are missing); however the book is not intended to be a literature compendium but an introduction, stimulation and reference work for the planning and execution of one's own experiments.

Three chapters cover the theoretical basis: the modified Bloch equations for exchange, the application of density matrix formalism to coupled spin systems, the theory of T_1 and T_1 and saturation transfer experiments. The density matrix chapter assumes knowledge of the quantum mechanical description of NMR spectra and linear algebra. A large proportion of interested chemists will probably omit these sections and utilize the currently available computer programs on a "black box" basis.

The following three chapters introduce the practice of spectrum recording and analysis. Thus, sample production, choice of solvent, temperature measurement, line shape evaluation using approximation formulas or total line shape simulation and statistical and systematic errors in activation parameters are among the subjects that are given a detailed and competent treatment. This central section of the book together with the next two chapters. covering specialized techniques (the application of lanthanoid shift reagents, ^{13}C-DNMR, DNMR in the gas phase, etc.) and worked out examples, constitute the most impressive part of the book. A great deal of information scattered throughout individual publications, is summarized here. Even readers already experienced in DNMR spectroscopy will come across some useful information.

The latter part of the book is an introduction to computational methods for the determination of activation barriers. Alongside a short synopsis of quantum mechanical calculations, force field calculations are presented for pseudorotation in ring systems and for rotation in triarylmethyl compounds.

"Sandström" is a book that should be on everyone's desk who is a starter in dynamic NMR spectroscopy. Had

such a book been available in the infancy of DNMR spectroscopy then a large proportion of the false enthalpies and entropies of activation that have given DNMR spectroscopy its reputation for inaccuracy would never have been published.

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Membranbiochemie. By *H. Sandermann*. Springer-Verlag, Berlin 1983. v, 131 pp., bound, DM 44.00.

Membrane biochemistry sounds attractive.—The author promises an introduction at the molecular level to biological processes in and at membranes, with emphasis on the properties of the proteins, the lipids, and the polysaccharides bound to them. The book is intended as a university text for students who have completed a basic course in biochemistry and wish to know more about the molecular aspects of membranes, a topic that usually receives only a short treatment in biochemistry textbooks. The requirement is there; one is full of wonderment as to how the topic will be treated in 125 pages.

Many key words of membrane investigation are sketched out in ten chapters: types of membranes, membrane isolation, structure and properties of lipids and biological membranes, methodological approaches to the study of membranes, detergents, membrane proteins including their biosynthesis and isolation, lipid protein interactions, transport through membranes, regulation of the activity of membrane-bound enzymes, chemiosmosis and ATP production, the importance of the polysaccharides on the cell surface including the biosynthesis of glycoproteins and as far as the metabolism of environmental chemicals.

In view of the size of this little book the abundant and highly interesting range of topics damps expectations from the start: it can only consist of a synopsis, which provides the student with key words and hints for further reading—which is no bad thing in itself.

Here, however, one of the failings of the book becomes evident: there is a dearth of references. Methodological approaches to membrane and protein isolation are sketched using several examples. The labeling of a method with a name or a classification as a pioneering piece of work is of little use to the reader. Experimental data, thermodynamic quantities and their interpretation originating from a topical and continually changing area of investigation must be made capable of being placed chronologically and subjected to verification by quoting their sources. This is of particular importance when, as on p. 64, models and analysis are contradictory or various models are compared. Alone the sources of figures are quoted in the figure legends. The general reference to two review journals at the end of the book is valueless without further specification. Standard biochemistry textbooks cannot be recommended for *further reading*, since this little book is intended to supplement them.

The book is derived from a course of lectures and is in its first edition. Because of this there are mistakes; however, they pass the bounds of the acceptable: printing errors, forgotten or wrong units, unacceptable abbreviations and units, errors in chemical formulas and incorrect labeling of axes characterize the book and bewilder the student.

In addition to this there are, particularly in the physicochemical observations, imprecisions of language and confusing argumentations. Unexplained and uncheckable values, as for example on p. 109 concerning the statistics of hexose combinations, should be avoided. Displaced and irregular print in almost all the mathematical formulas make reading more difficult.

What a pity—a good idea, a good beginning, very well chosen material. The strength of this book lies in the descriptive biochemical-biological aspects. The molecular principles, reproduced through physical-biochemical considerations, leave much to be desired, and there is a lack of clear presentation. Perhaps this little book is a beginning; it is certainly not a matured textbook and at a price of 44 DM cannot be recommended to university students, at least in its present form.

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Elementary Statistical Thermodynamics. A Problems Approach. By *N. O. Smith*. Plenum Press, New York 1982. xiv, 216 pp., bound, $ 25.00.

Much of the evidence concerning the properties of molecules and their behavior depends on the application of statistical thermodynamics. It should therefore occupy a relevant place in the education of chemists. One of the reasons why this is not universally true may well be that access to this field is not particularly easy: Firstly it is not immediately obvious to the student how the chances of a gambler in a numbers game are related to the specific heat of an alcohol or the lifetime of an activated complex. It is not surprising that American authors in particular attempt to provide students with as smooth an entry as possible into statistical thermodynamics. This little book is an example of a compromised attempt: Some knowledge of chemical thermodynamics, simple functions, differentiation and integration, the treatment of series and some combinatorial analysis is assumed. Even the reminder that $0! = 1$ has not been forgotten. The author employs IUPAC nomenclature and SI units.

The individual chapters of the book cover the usual topics: The statistical mechanics of distinguishable particles; the statistical basis of entropy; thermodynamic functions for systems of localized and distinguishable particles (with the Einstein and the Debye crystal models); systems of non-localized and indistinguishable particles; the thermodynamic functions of ideal gases: Here there is a careful explanation of translational, rotational, vibrational and electronic partition functions, the contribution of the atomic nucleus, ortho- and parahydrogen, and of the influence of internal rotation. This is followed by the statistical thermodynamic calculation of chemical equilibria.

Each chapter is accompanied by cleverly chosen exercises, which not only improve understanding of the basic material but also communicate a feeling for the magnitudes of the relevant thermodynamic probabilities, partition functions, entropies, etc. Some of the exercises are worked through in the text, the solutions to the others are included in an appendix.

The book seems to incorporate a great deal of teaching experience. It can be recommended as an introduction to students of chemistry and other sciences who have sufficient knowledge of English—it is also suitable as a "teach

yourself" book. The price may well ensure a certain exclusivity.

Heinz Georg Wagner [NB 625 IE]
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DNA Methylation: Site-Specific Methylations Cause Gene Inactivation

By Walter Doerfler*

In the molecular biology of eukaryotic organisms, the elucidation of mechanisms involved in the regulation of gene expression has assumed an important role. All cells of an organism carry the same genes, but differ in the patterns of genes they express. There is an increasing amount of evidence that cancer cells exhibit a pattern of gene expression which can be very different from that of normal cells. One of the molecular signals that has been recognized in the regulation of gene expression in eukaryotes is the modified nucleotide 5-methylcytosine (5-mC). Through experiments in well-characterized eukaryotic systems, evidence has been adduced that the introduction of 5-mC into highly specific sequences, particularly into the 5′ and promoter regions of a gene, can cause gene inactivation. Viral and other eukaryotic systems have helped in the recognition of this cause-and-effect relationship. Inactive genes are frequently hypermethylated in the promoter region; active genes are hypomethylated. However, these correlations are not always as simple and straightforward. The biochemical mechanisms by which site-specific DNA methylations cause gene inactivation have not yet been determined. It is plausible to postulate that promoter methylations could somehow affect the binding of cellular enzymes involved in recognizing the promoter of a gene. Structural alterations of DNA promoter sequences arising from DNA methylations could also be important. DNA methylation is likely to represent a long-term inactivation signal, since it is presently thought that patterns of DNA methylation can be changed only by DNA replication and specific inhibition of post-replicative maintenance methylation.

1. Introduction

The primary genetic code, the nucleotide triplets in deoxyribonucleic acid (DNA), and its coding function for amino acids in proteins have been deciphered practically completely[1]. In comparing genetic coding principles with those known from linguistics[2], one could equate, metaphorically, the primary genetic code to the vocabulary of a language. Knowledge of the vocabulary of a language, however, does not provide any inkling of its grammar and syntactic intricacies. Similarly, the primary genetic code lacks a description of the rules that dominate the expression of the genetic text and its regulation. It has proved a major task, occupying a sizeable portion of current research in molecular biology, to recognize regulatory signals in the more complex part of the genetic code (secondary and tertiary coding principles). Particularly in higher organisms, the eukaryotes, these regulatory principles of the genetic code appear to be complicated and have not yet been completely unravelled. In this overview article, I shall concentrate on the evaluation of one—seemingly simple—genetic signal: the modulating function of the modified nucleotide 5-methylcytosine (5-mC). There is considerable experimental evidence derived from many different eukaryotic systems which indicates that, as a constituent of specific nucleotide sequences, 5-mC can play an important role in the long-term inactivation of eukaryotic genes[3–6].

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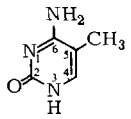
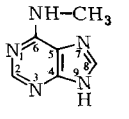
The coding and signal values of the four deoxyribonucleotide bases adenine, cytidine, guanine, and thymidine in naturally occurring DNAs can be complemented by specific modifications of some of these nucleotides. The modified nucleotides found in DNA are 5-mC and N^6-methyladenine (N^6mA). The occurrence of additional modifications cannot be ruled out, but they are extremely infrequent and not detectable by the techniques usually employed (see Section 2).



5-Methylcytosine (5-mC)



N^6-Methyladenine (N^6mA)

DNA obtained from prokaryotes can contain 5-mC and N^6mA. In the DNA of higher eukaryotes 5-mC is the predominant modified nucleotide. The biological functions of 5-mC and N^6mA have long been enigmatic. The most clearly established role that DNA modifications have been shown to play is in their generally protective effect against the activity of restriction endonucleases in microorganisms[7]. In almost all instances, restriction endonucleases[8] cannot cleave DNA at nucleotide sequences that have been specifically methylated (Table 1), since interaction between restriction endonucleases and DNA is no longer possible. However, there are interesting exceptions to this "rule". The restriction endonuclease pair *Dpn*I and *Dpn*II from *Diplococcus pneumoniae* are isoschizomeric in that they recognize and cut at the nucleotide sequence 5′-GATC-3′. *Dpn*I is dependent for its activity on the presence of N^6mA in the recognition sequence, whereas *Dpn*II is completely inhibited by the modified nucleotide[9] (Table 1). This example serves to demonstrate that the biological function of a small modifying signal, such as the methyl group in N^6mA or 5-mC, can exert a positive or negative effect on the interaction between specific proteins, in this instance restriction endonucleases and DNA. Thus, the directional significance of this functional modifier is not uniquely determined a priori and seems to depend crucially on the nucleotide sequence and the specific type of protein-DNA interaction it is going to influence.

Table 1. Restriction endonucleases are inhibited by sequence-specific DNA methylation [a].

Enzyme	Source	Recognition sequence [b]	Modified sequence refractory to cleavage
a) 5-mC Sensitive			
*Hha*I	*Haemophilus haemolyticus*	GCG$^{\downarrow}$C	G^{m}CGC
*Hpa*II [c]	*Haemophilus parainfluenzae*	C$^{\downarrow}$CGG	C^{m}CGG
*Msp*I [c]	*Moraxella species*	C$^{\downarrow}$CGG	^{m}CCGG
*Bsu*RI	*Bacillus subtilis* R	GG$^{\downarrow}$CC	GG^{m}CC
b) N^6mA Sensitive			
*Eco*RI	*Escherichia coli* RY 13	G$^{\downarrow}$AATTC	GA^{m}ATTC
*Mbo*I	*Moraxella bovis*	$^{\downarrow}$GATC	G^{m}ATC
*Dpn*I [c]	*Diplococcus pneumoniae*	G^{m}A$^{\downarrow}$TC (!)	GATC (!)
*Dpn*II	*Diplococcus pneumoniae*	GA$^{\downarrow}$TC	G^{m}ATC
*Taq*I	*Thermus aquaticus* YTI	T$^{\downarrow}$CGA	TCG^{m}A

[a] This table shows examples of methylation-sensitive restrictases. [b] The sequence for one strand is presented in 5′→3′ direction. The vertical arrow designates the phosphodiester bond which is cleaved. All sequences presented are palindromic. [c] Isoschizomeric pair of restrictases which recognize and cleave at the same sequence.

DNA methylation or alterations of specific patterns of DNA methylation have also been implicated to play a role in the repair of DNA, in genetic recombination, in virus latency, in differentiation, in the inactivation of one of the X chromosomes, and possibly in the alterations leading to the transformation of normal cells into cancer cells. In particular, in the more complex biological processes mentioned it is likely that changes in the patterns of DNA methylation directly or indirectly affect the expression of specific genes or of sets of genes. Altered expression patterns of a cell may then cause or be related to more complex changes in the functional phenotype of differentiated cells and cancer cells.

In this review article the evidence will be summarized that has led to the hypothesis that in the higher eukaryotes DNA methylations at highly specific sequences in the promoter and 5′ regions of a gene can lead to its inactivation. It will be apparent from the preceding discussion that the gene inactivating effect of 5-mC can be mediated by modulating specific protein-DNA interactions at specific sequence motifs in the promoter site of a gene (see Fig. 1), by structural alterations of the DNA or by a combination of both. Since demethylation of DNA has as yet not been established, patterns of DNA methylation can only be changed by DNA replication and concomitant inhibition of maintenance DNA methyltransferases (see Section 2). It is therefore plausible to assume that methylations of specific nucleotides in the promoter sequence of a gene will lead to its long-term inactivation. In this context, it is important to realize that a gene can also be inactivated without promoter methylation, e.g. simply due to specific protein-DNA interactions at certain promoter sites. The additional measure of methylation of promoter sites would probably safeguard this inactivation and would render it long-term. Clearly, unmethylated promoter sites do not guarantee gene activity: "An unlocked door is not necessarily open"[10].

The number of publications on DNA methylation and its possible biological functions has grown rapidly in recent years, and I do not intend to present a complete survey of this exciting field. Many review articles on DNA methylation have been published[3-6, 10-18] and three monographs edited by *Taylor*[19], *Trautner*[20], and by *Razin, Cedar,* and *Riggs*[21] have appeared. There is no need to duplicate these efforts. I shall concentrate instead on recent developments and future trends in the field.

2. Basic Facts about DNA Methylation

Methods used to determine methylated bases in DNA are summarized in Table 2. In the DNA, particularly of the higher eukaryotes (vertebrates), 5-mC is predominantly found in the dinucleotide sequence CpG and less frequently in the dinucleotide combinations CpC CpT or CpA[29]. In mammalian DNA up to 90% of the 5-mC residues are found in the dinucleotide CpG. It is interesting to note that this dinucleotide is statistically strikingly under-

Table 2. Methods of determining methylated bases in DNA.

1) Acid hydrolysis of DNA followed by
   a) Two-dimensional chromatographic or chromatographic and electrophoretic procedures [22]
   b) High-pressure liquid chromatography, e.g. [23]
   c) Mass spectrometry
   Disadvantages: low sensitivity, fails to detect sequence specificities.
2) Analysis by methylation-sensitive restriction endonucleases coupled with Southern transfer [24] and DNA-DNA hybridization.
   a) isoschizomeric restrictases [25] [a]
   b) single restrictase [b]—comparison with cloned gene [4]
   Disadvantages: analysis limited to certain sequences. Does not detect all 5-mC residues.
3) Genomic sequencing method [26]
   Direct determination of all 5-mC residues in a DNA sequence.
   Disadvantage: analysis limited to short sequences (ca. 100 to 200 nucleotides).
4) Immunologic methods—antisera against 5-mC.
   Disadvantag: questionable specificity.

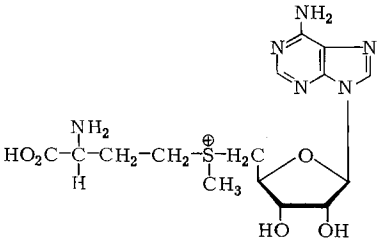
[a] Cellular DNA is cleaved by *Hpa*II or *Msp*I (Table 1), which both cut at 5′-CCGG-3′ sequences. 5′-C^{m}CGG-3′ is refractory to *Hpa*II, 5′-^{m}CCGG-3′ to *Msp*I. Thus it is possible to distinguish 5′-CCGG-3′ sequences from methylated forms of the same sequence. Upon cleavage, DNA fragments are separated by electrophoresis on agarose or polyacrylamide gels, transferred [24] to nitrocellulose filters, and specific sequences are recognized by hybridization to the [^{32}P]-labeled [27], cloned gene followed by autoradiography.—[b] For most sequences containing 5-mC, isoschizomeric restrictase pairs are not available. To a certain extent, one can still recognize these modifications by using restriction endonucleases. The gene to be analyzed has to be cloned and propagated in a C methylation-deficient (mec$^-$ [28] host. The cleavage pattern of the cloned, unmethylated gene is then compared to that of the genomic sequence. E.g.: Methylation of the 5′-GCGC-3′ sequence (5′-G^{m}CGC-3′) can be determined by using the methylation-sensitive restriction endonuclease *Hha*I.

represented in the DNA of eukaryotes[30]. In vertebrates the CpG dinucleotide accounts for 1% of all dinucleotides, whereas statistics would predict 4%. In general, the nucleotide sequences in nature are not assembled statistically, but are highly selected products of millenia of functional optimization. The statistical counter-selection of the CpG dinucleotide in the DNA of eukaryotes suggests that it has a special functional significance. This hypothesis is further enhanced by the finding that the CpG dinucleotide is also the main site of modification by methylation which can lead to inactivation of gene expression.

It has been proposed that the underrepresentation of CpG dinucleotides in the DNA of vertebrates arises because of the high degree of methylation of the cytosine residue in this dinucleotide and the propensity of 5-mC to be deaminated to thymidine. This leads, of course, to the loss of a CpG dinucleotide and its conversion into TpG[31]. On the other hand, in prokaryotes CpG underrepresentation is not found, hence it is difficult to envisage that the deamination hypothesis provides an explanation for the underrepresentation of the CpG dinucleotide.

Although the CpG dinucleotide is drastically underrepresented in vertebrate DNA, clusters of CpG dinucleotides have been observed at the 5′ end of the globin gene[32] and at the 5′ and promoter end of the E1 region of adenovirus type 12 (Ad12) and adenovirus type 2 (Ad2) DNA[4,33]. CpG clusters also occur strikingly frequently around the polymorphic exons of genes of the major histocompatibility complex (MHC) in mouse and man, and at the 5′ end of the mouse dihydrofolate reductase gene and of the chicken α 2-collagen gene[34]. One can only speculate about the significance of these CpG clusters.

DNA methylation is a post-replicative event catalyzed by specific enzymes, the DNA methyltransferases. Some of these DNA methyltransferases from prokaryotes have been highly purified and well characterized, but much less is known about DNA methyltransferases in eukaryotes



S-Adenosylmethionine (SAM)

(see [11,35]). DNA methyltransferases utilize *S*-adenosyl methionine (SAM) as a methyl donor. Functionally, two types of DNA methyltransferases can be distinguished: 1) de novo DNA methyltransferases methylate specific sequences of previously unmethylated DNA; 2) maintenance DNA methyltransferases recognize hemimethylated DNA, i.e. a double-stranded DNA molecule with methyl groups in only one of its strands. Such a hemimethylated DNA duplex is generated, e.g., by one round of DNA replication leaving only one strand methylated. Maintenance DNA methyltransferases recognize methylated bases in hemimethylated DNA and attach a methyl group to the cytidine residue in the symmetrically-opposite position in the complementary DNA strand (Fig. 1). It is not known whether the two types of DNA methyltransferase activities reside in the same enzyme or represent separate entities.

Direct evidence for the occurrence of de novo methylation in eukaryotes comes from a viral system. Viral systems

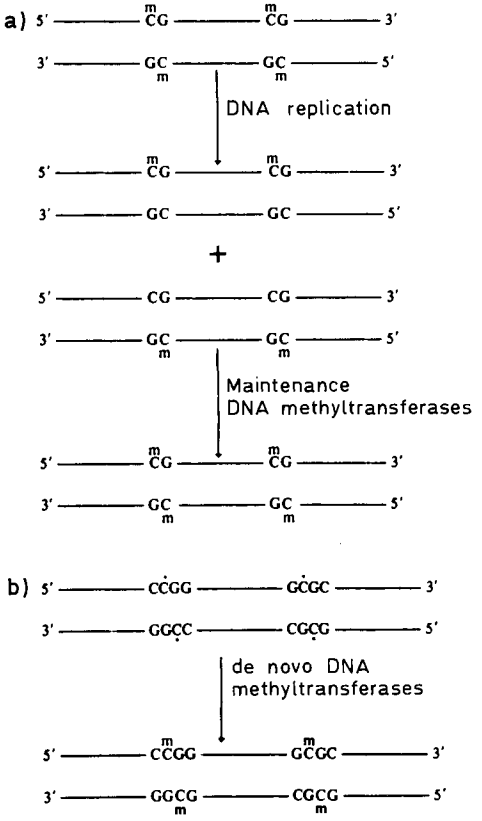


Fig. 1. a) Maintenance and b) de novo DNA methylation [5].

have played an important role in elucidating the function of sequence-specific DNA methylations in vertebrate systems[4]. The DNA of the human adenoviruses, for example, is methylated only when the viral DNA has been integrated into the DNA of the host and has persisted in that state for some time[36–38]. DNA isolated from the virion (virus particle)[22, 23, 39] or extrachromosomal forms of intracellular viral DNA are not methylated (Table 3)[40, 41]. It is therefore compelling to conclude that adenovirus DNA must have undergone de novo methylation some time after integration[46–48] into the DNA of the host cell. It still remains an enigma how the host-DNA-methyltransferases are instructed to highly specifically methylate the foreign, viral DNA molecules previously inserted into the host DNA[42, 43, 45]. Since the parental viral DNA was devoid of 5-mC groups, the methylation had to be de novo.

Table 3. DNA methylation of the genome of human adenoviruses [a].

Type of adenovirus DNA	State of methylation	Ref.
DNA packaged into virus particles	Unmethylated [b]	[22, 23, 39]
Free viral DNA in infected mammalian cells (productive and abortive systems) both parental and newly synthesized	Unmethylated	[40, 41]
Integrated adenovirus DNA in established cell lines	Methylated in highly specific patterns: Active genes are hypomethylated; inactive genes are hypermethylated	[40, 42—45]
Integrated adenovirus DNA in recently produced tumor cells	Hypomethylated. Gradual increase in DNA methylation with passage of tumor cells. Shift in methylation is nonrandom	[37, 38]

[a] The only methylated base detectable is 5-mC [22, 23]. [b] Limit of detectability <0.04% 5-mC [23].

It should be mentioned that the genomes of some cytoplasmic DNA viruses, e.g. of the iridovirus FV3 (frog virus 3), are highly methylated (>20% of all C residues are 5-mC)[49]. There is evidence that FV3 can code for its own DNA methyltransferase, which modifies viral DNA in the cytoplasm of the infected cell[50].

It is important to investigate whether eukaryotic cells have an (enzymatic) mechanism of active demethylation. One report[51] has appeared describing demethylating activity in the nucleus of murine erythroleukemia cells. If a demethylating activity did not exist, the only way of altering patterns of methylation by removal of methyl groups would be DNA replication and concomitant specific inhibition of the maintenance DNA methyltransferases. The element of specifically altering patterns of methylation would remain a puzzle even if a "demethylase" were found.

There is still another problem to be considered. Evidence has been adduced[52] that DNA replication in mammals is temporally bimodal. A certain group of genes, the so-called household genes, which function in practically every cell, replicate during the first half of the S phase of the cell cycle. Tissue-specific genes, which are expressed only in certain organs, e.g. the insulin gene in the β cells of the Langerhans islets in the pancreas, replicate early in those cells in which they are expressed and late in tissues in which they usually are not. As a consequence of those temporally highly specific patterns of replication of certain groups of genes, these may become transiently hemimethylated (cf. Fig. 1), at least until they are fully re-methylated by maintenance DNA methyltransferase. The question arises whether during the transient state of hemimethylation the genes could be expressed for a short period of time. Thus, even for "inactive genes" in the classical sense of this concept there may be a narrow temporal window during which they could become active. For the further investigation of this concept, it will be important to determine whether hemimethylated genes are active or inactive.

A number of laboratories are now actively pursuing the possibility that specific DNA methylations may alter highly selective protein-DNA interactions. Recently, a protein from human placenta has been purified that binds somewhat better to 5-mC-rich DNA sequences[53]. Undoubtedly, there is already a flourish of experimental activity in this interesting field of biochemistry.

3. The Basic Structure of Eukaryotic Genes

Some of the concepts to be developed in this review article will be more readily comprehensible if the basic structure of the eukaryotic gene is first described[54, 55]. Eukaryotic genes consist of a control region located at the 5′ end of the DNA and the gene proper, the body of the gene, located at the 3′ end (Fig. 2). The designations 5′ and 3′ re-

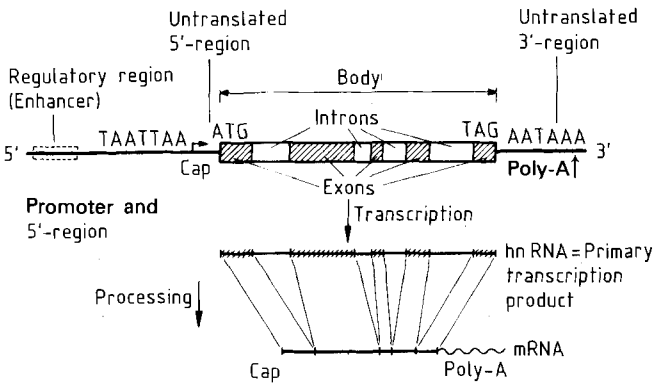


Fig. 2. Schematic representation of the basic features of eukaryotic genes, including transcription and processing of the RNA.

late to positions on the plus[*] strand of the DNA molecule, conventionally written 5′→3′ from left to right, as European languages are written. That part of the control region responsible for binding the transcribing enzyme(s) is called the promoter. The control region is characterized by several features, the TAATAAA (Hogness-Goldberg) box, the cap site (initiation of transcription), and the upstream (5′) controlling elements. These motifs have been shown to be essential for gene expression, some of them presumably functioning by mediating specific protein-DNA interactions, but their exact biochemical functions are not yet

[*] By definition the plus strand of DNA has the same sequence as mRNA.

known. The body of the eukaryotic gene has 5′ and 3′ untranslated regions attached which do not code for protein sequences. At the 3′ end of the gene is situated an ATAAA signal which is involved in specifying the addition of a polyadenylic acid tail to the messenger RNA. The body of a gene consists of introns (intervening sequences) which are spliced out during processing of the primary transcription product (hnRNA = high molecular weight heterogeneous nuclear RNA) to messenger RNA. The exons (expressed sequences) are spliced together during processing of hnRNA to the functional messenger RNA molecule which is actually translated, beginning at the first functional AUG triplet. In a rigorous definition, it is only the sum of the linked-up exons which constitutes the functional gene, because the message is eventually translated into a polypeptide sequence. The role played by the 5′ untranslated sequence (between the cap site and the ATG initiation codon) and of the 3′ untranslated sequence (beyond the termination codon) is not well understood. The DNA sequences that are functionally modulated by site-specific methylation, thus leading to inactivation of genes, reside in the promoter and 5′ sequences of genes.

4. What Evidence Led to the Concept that DNA Methylation Can Cause Gene Inactivation?

The first speculations relating DNA methylation to the control of gene activity date back to 1964[56] and emanated from work on bacterial systems. More clearly defined hypotheses formulated in 1975 were related to higher eukaryotes[57–59]. Shortly thereafter, experimental evidence was obtained which directly supported the view that inactive genes were hypermethylated and active genes, hypomethylated. *Inverse correlations* of this type[43] were observed in quite different eukaryotic systems in a large number of laboratories. Since the experimental development of these ideas has been extensively reviewed[3–6], I shall only briefly summarize the results.

4.1. Inverse Correlations between DNA Methylation and Gene Expression

Inverse correlations between the extent of DNA methylation and the level of expression of a given gene have been established by analyzing a number of eukaryotic and viral genes in different systems. Since these correlations have so far been mainly restricted to 5′-CCGG-3′ and 5′-GCGC-3′ sequences, it cannot be expected that they apply without exceptions to all the genes investigated since other CG-containing sequences might also be involved. The establishment of such inverse correlations does not, however, allow statements to be made on whether DNA methylation is the cause or the consequence of gene inactivation.

Experimental evidence for such inverse correlations was provided by studies on DNA methylation of a certain gene in different organs of one organism and by studies on viral systems[37,42–45,60–72]. Viral systems yielded strikingly clear results. For a given gene that was actively expressed in one organ, many of the 5′-CCGG-3′ sequences were found to be unmethylated, whereas the DNA in the same gene in other organs where it was not expressed was completely methylated at these sequences.

In integrated viral genomes, unexpressed genes were hypermethylated, while transcribed genes showed low levels of methylation. In Table 4 examples of cell lines transformed by adenovirus type 2 are shown in relation to the expression and methylation of the E2a gene of adenovirus type 2 DNA[40]. The 5′-CCGG-3′ sequences were investigated because of the availability of the isoschizomeric restriction endonuclease pair *Hpa*II and *Msp*I[25], which permitted determination of the state of methylation at all the 5′-CCGG-3′ sites. In many genes this state of methylation appears to have special significance. In some cases[37,45], these inverse correlations have been extended to other sequences containing 5′-CpG-3′ dinucleotides, e.g. the sequence 5′-GCGC-3′, the recognition sequence of the restriction endonuclease *Hha*I.

Table 4. Inverse correlations between DNA methylation and E2a expression in cell lines HE1, HE2, and HE3.

Cell line [73]	E2a gene and late promoter [44] persisting in integrated form	mRNA [74]	E2a protein [75]	Methylation [40] of 14 CCGG sites in E2a gene
HE1	+	+	+	−
HE2	+	−	−	+
HE3	+	−	−	+

As expected, inverse correlations between gene activity and DNA methylation at 5′-CCGG-3′ and 5′-GCGC-3′ sequences do not invariably exist. Such apparent discrepancies lack significance unless substantiated by very careful analyses of the gene investigated. In some genes DNA methylation at sites other than *Hpa*II or *Hha*I sites may be important for regulation. Unusual methylation patterns with respect to expression have been reported for the estrogen-inducible vitellogenin genes A1 and A2 in the hepatocytes of *Xenopuls laevis*[76]. These genes are heavily methylated irrespective of expression, while other Xenopus laevis genes show the usual inverse correlations.

4.2. Studies on Expression of in vitro-Methylated Genes

The establishment of correlations raises interesting questions in biology, but does not help to determine a cause-and-effect relationship. In order to resolve whether DNA methylation was the cause or the consequence of gene inactivation, in vitro-methylated cloned genes were microinjected into the nuclei of Xenopus laevis oocytes[77–81] or into mammalian cells in culture[82–84] and the activities of these genes subsequently studied. Genes methylated at specific sites were not expressed. The use of sequence-specific de novo DNA-methyltransferases from prokaryotic organisms allowed the determination of highly specific sequences involved in the control of gene expression. Other sequences, e.g. the 5′-GGCC-3′ sequence methylated in vitro, did not exhibit any effect on gene expression[33,79]. These data derived from studies of different systems in different laboratories provided direct support for the concept that methylated sequences at highly specific sites play an

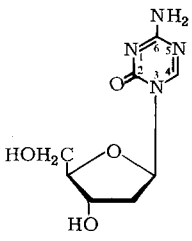
important role in the regulation of gene expression. Furthermore, these observations demonstrated that DNA methylation caused transcriptional inactivation, at least in the genes studied, and was not a consequence of gene inactivation.

Other authors[85] used a DNA methyltransferase from rat liver which methylated all 5′-CpG-3′ dinucleotides in a Moloney murine leukemia proviral DNA clone. The biological activity of the methylated clone was found to be reduced by three orders of magnitude in transfection assays, whereas methylation of thirty-five 5′-CCGG-3′ sites by the prokaryotic *Hpa*II DNA methyltransferase had a lesser effect. However, in vitro methylation of all the CpG dinucleotides of polyoma DNA and SV40 DNA by the same rat liver enzyme led to viral DNAs which were still fully infectious[86]. In these experiments, however, it could not be ruled out that the transfected DNA had replicated and thus had become demethylated. When the cloned murine leukemia provirus was methylated with *Hpa*II DNA methyltransferase, it was also only slightly inactivated[71]. It is apparent that the sequences susceptible to methylation may be quite different for individual genes.

From our own contributions to this particular problem, it appeared important that work on the in vitro methylation of adenoviral genes be preceded by a thorough investigation of the state of methylation of the same gene in the integrated form in transformed cells[40,43,45]. Since only two DNA methyltransferases, *Hpa*II and *Hha*I, were available for these studies, we had to ascertain whether the 5′-CCGG-3′ and 5′-GCGC-3′ sites were actually involved in the regulation of this particular gene. Thus, in vivo studies proved to be an important prerequisite for the successful design of in vitro investigations. Moreover, it was essential to ascertain that in vitro DNA methylation of a gene was complete before attempting to test its transcriptional activity. Complete methylation was tested by cleavage with *Hpa*II, *Msp*I, or *Hha*I, followed by Southern[24] blotting and hybridization. As discussed in Sections 5 and 6, in vitro specific DNA methylation and the ensuing analyses of the effects of these modifications on gene expression has been refined by methylating only specific parts of genes.

4.3. Inhibition of DNA Methyltransferases by 5-Azacytidine

Further evidence for the role played by DNA methylation in the regulation of gene expression comes from studies with the cytidine analogue 5-azacytidine (deoxyribonucleoside).



5-Azacytidine
(Deoxyribonucleoside)

This modified nucleoside can be incorporated into replicating DNA, but cannot be methylated in the 5-position. However, the main inhibitory role of 5-azacytidine toward DNA methylation stems from its ability to inhibit DNA methyltransferases[87-90]. In a number of different systems it has been possible to activate dormant genes and to induce their expression[90-94]. The original report on the gene activating property of 5-azacytidine described the activation of a complex set of cellular functions leading to in vitro differentiation of mouse fibroblasts to muscle cells which were shown to contract in culture[95]. Specific genes could be turned on even in animals by treatment with 5-azacytidine[96] and in humans[97]. In this way fetal hemoglobin synthesis was stimulated in anemic baboons and γ-globin synthesis selectively increased in patients with β^+-thalassemia. Concomitant demethylations in the genes involved could also be shown[97]. Since 5-azacytidine is a highly toxic agent, patients must not be treated without carefully weighing the risks and benefits in each individual case.

It is not to be expected that all dormant cellular genes can be reactivated by treating cells with 5-azacytidine. Absence of DNA methylation appears a necessary but not a sufficient condition for gene activation[37,67,98,99]. A mechanism as essential as gene activity is probably subject to several regulatory mechanisms, DNA methylation being one important parameter. Thus, depending on the stringency of inactivation for a given gene, 5-azacytidine treatment may or may not lead to the activation of a certain gene or set of genes. For example, in an Ad12-transformed hamster cell line (T637), the inactive and hypermethylated late viral genes, which are integrated into the host genome, could not be activated by 5-azacytidine, although changes in patterns of DNA methylation were detected[33]. The results obtained by 5-azacytidine induction are interesting but are also problematic to some degree, since a toxic analogue could always have additional, poorly understood effects, and the interpretation of the induction phenomena may be more complicated than previously thought.

Interestingly, in vitro studies using DNA methyltransferase from mouse spleen indicate that chemical carcinogens inhibit the transfer of methyl groups to hemimethylated DNA. Perhaps carcinogenic agents might lead to heritable changes in DNA methylation patterns by a variety of mechanisms[100] and thus alter the patterns of gene expression in cancer cells (see Section 8.3).

5. The Promoter and the 5′ End of Genes are Sensitive to DNA Methylation

In several eukaryotic and viral systems, absence of DNA methylation at the 5′ ends and/or promoter sites of genes correlates with the active state of genes[45,98,99,101-105]. The vitellogenin gene in chickens could be activated by treatment with estrogen, the activation being accompanied by demethylation of a 5′-CCGG-3′ site at the 5′ end of this gene[104]. Since the decisive interactions between the DNA sequence of a gene and the transcriptional machinery of the cell have to occur at the promoter and 5′ end, DNA methylation should affect gene expression chiefly at these sites. Within the promoter region different sequences could be important for the regulation of individual genes.

We have analyzed in detail the state of methylation of a large number of 5′-CCGG-3′ and 5′-GCGC-3′ sequences in

integrated adenovirus genes in three different Ad12-transformed hamster cell lines[45]. Most of the early viral genes are expressed in these cell lines (horizontal arrows in Fig. 3), and the 5′ and promoter regions of these genes are unmethylated at the 5′-CCGG-3′ (◇ in Fig. 3) and 5′-GCGC-3′ sequences (not shown in Fig. 3). The states of methylation of the 3′-main parts of the early viral genes do not correlate with their activity. The 5′-CCGG-3′ and 5′-GCGC-3′ sequences in the integrated late viral genes, which are not expressed, are all methylated[43] (data not shown in Fig. 3). In the cell line HA12/7 (Fig. 3), the E3 region is not expressed (no horizontal arrow), and accordingly the 5′-CCGG-3′ (and 5′-GCGC-3′) sequences at the 5′ and promoter ends of this region are all methylated.

of these cells. Thus, those cells in which the methylation patterns of viral genes assured permanent inactivation of late viral genes were selected as the stably transformed cells. This particularly stringent mode of selection might explain the very striking inverse correlations between DNA methylation and gene activity described for many integrated viral genes[4].

6. Effect of in vitro Methylation of the Promoter and 5′ Ends of Eukaryotic Genes

The importance of the promoter region in DNA methylation and gene inactivation can be demonstrated experi-

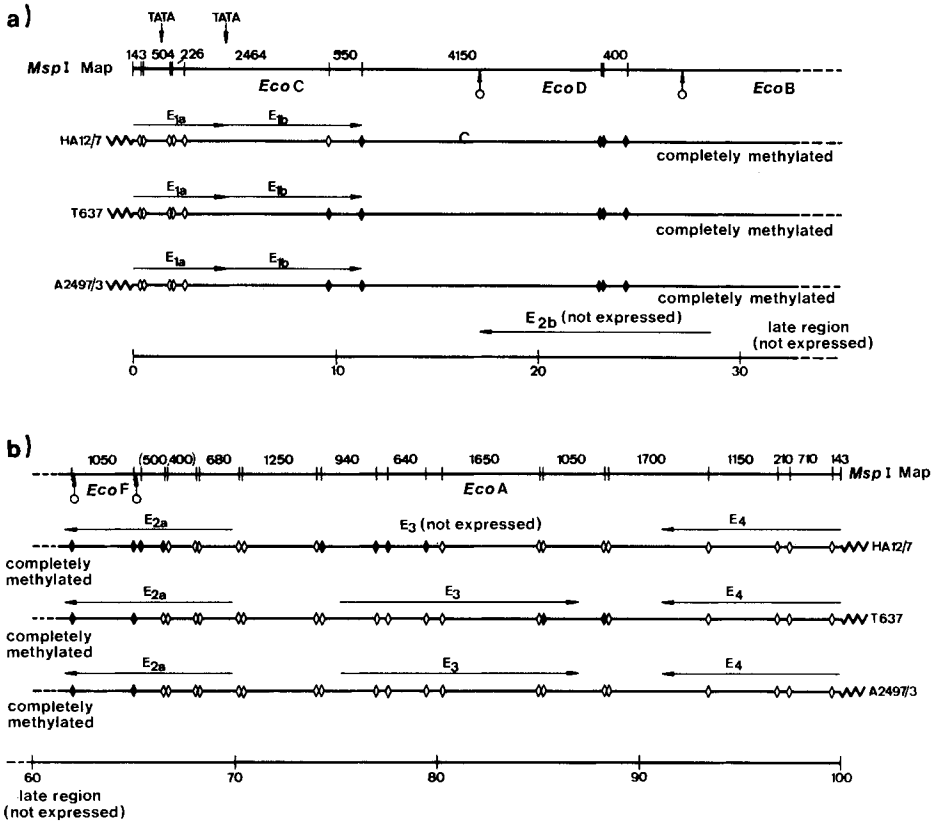


Fig. 3. Functional maps of the left (a) and the right (b) halves of the adenovirus type 12 DNA molecule integrated into cell lines HA12/7, T637, or A2497-3. The horizontal lines represent the Ad12 genomes (—) integrated into the genomes of cell lines (〰) as indicated. The *Msp*I maps of the left (a) and right (b) ends of Ad12 DNA are represented in the top line. Vertical bars on and figures above the horizontal lines indicate the locations of the *Msp*I sites and the sizes of some of the *Msp*I fragments, respectively. The symbols (δ) designate *Eco*RI sites. TATA marks the locations of presumptive Goldberg-Hogness signals in the E1a region. The unmethylated and methylated 5′-CCGG-3′ sites in the integrated Ad12 genomes in the lines HA12/7, T637, and A2497-3 are designated by open (◇) and closed symbols (◆), respectively. The horizontal arrows indicate map positions and the directions of transcription of the individual early regions in each of the cell lines. The presence of an arrow indicates expression of corresponding regions of the Ad12 genome. *Msp*I sites to the right of the *Eco*RI-D/B and to the left of the *Eco*RI-A/F junctions have not been mapped. The early regions of Ad12 DNA [106, 107] are also indicated. The scales at the bottom of each figure show the lengths of fractional units of the viral genome subdividing the molecule into 100 equal units. The map of the E1 region of Ad12 DNA is as described in [108]. This figure was taken from [45].

In viral systems, correlative studies on DNA methylation and gene expression have frequently yielded particularly clear results[4, 5]. Conceivably, in virus-transformed cells the late viral genes have to be inactivated and maintained in the inactive state by particular safeguards, e.g. by the introduction of methyl groups; otherwise, activation of these genes might lead to viral replication and destruction

mentally. The results of three different experimental approaches will be described here: 1) Methylation of the promoter region of the globin gene[109]. Upon insertion of the methylated gene into the genome of a recipient cell, the globin gene was inactive. In a similar experiment, the unmethylated globin gene remained active. 2) The E1a promoter of adenovirus type 12 DNA was inserted in front of

the chloramphenicol acetyl transferase (CAT) gene[102] in a construct[*], pSVO CAT, that permitted promoter insertion[110]. Upon transfection into mammalian cells, the unmethylated promoter was active; however, the 5′-CCGG-3′ or 5′-GCGC-3′ methylated promoter, was inactivated when the methyl groups were positioned upstream from the TAATAAA box. 3) We have tested the transcriptional activity of the cloned E2a gene of adenovirus type 2 after microinjection into oocytes of *Xenopus laevis*[77,78]. This gene encodes a DNA-binding protein[111]. When three 5′-CCGG-3′ sites in the 5′ region of the E2a gene were methylated, the gene was inactive after microinjection. Methylation of eleven such sites in the 3′ main part of the gene left its activity intact[105].

These results are consistent with the idea that the methylation of only very few nucleotides, perhaps only of one nucleotide, in a decisive region of the promoter can inactivate genes. Whether this also applies to other eukaryotic genes remains to be seen.

At this point an important caveat has to be mentioned: In designing in vitro methylation experiments, one must be careful in selecting the sequences that are methylated in vitro: Selection should be based on the results of analyses on the same gene in the inactive state as it exists in living cells. Only then, can one be certain that modified sites are formed that have a function in the permanent shut-off of that particular gene. As an example let us reconsider the E2a gene of adenovirus type 2 DNA (Table 4): In Ad2-transformed cells that do not express this gene, all fourteen 5′-CCGG-3′ sequences are methylated at the second C, suggesting, but not proving, a regulatory role for 5-mC in that sequence. In contrast, in Ad2-transformed cells that do express the E2a gene the same sites are unmethylated[40]. The results of the in vitro methylation experiments detailed in the following section, provide strong experimental evidence for the general concept and identify the 5′-CCGG-3′ sequences in the 5′ region, at least in this gene as decisive sites in gene regulation by DNA methylation. Haphazard approaches to in vitro methylation experiments, in particular with enzymes of as yet questionable specificity, may lack functional significance.

6.1. Inhibition of Transcription of the γ-Globin Gene by Specific Methylations of the Promoter

The complete methylation of CpG sequences in the 5′ region of the γ-globin gene between nucleotides −760 to +100 prevents its transcription[109]. There are eleven CpG dinucleotides in this stretch of 860 nucleotides. It has not yet been elucidated which of these nucleotides are decisive in shutting off gene expression. The authors used the in vitro methylation procedure[82] based on replicating a gene, in this case the γ-globin gene, in the single-stranded vector M13 in the presence of 5-methyl dCTP. By choosing the appropriate primer fragment for this in vitro replication reaction, specific segments of the gene and its flanking sequences can be methylated. In this way, the cytidine residues in a certain segment are methylated; this method therefore does not permit identification of the functionally significant nucleotides. The cloned γ-globin gene, various regions of which were thus hemimethylated, was then cotransfected into Ltk$^-$ murine cells, an established mouse cell line, with the thymidine kinase gene of herpes simplex virus. Cell clones containing both the γ-globin and thymidine kinase genes were selected. It was found that the CpG methylation pattern introduced in vitro was maintained in both strands of the gene and was faithfully inherited in this system, as previously reported for other genes[112]. Methylation in the region from −760 in the 5′ flanking region of the γ-globin gene suppressed globin expression, whereas methylation of C residues of the γ-globin gene (from +100 to +1950) in the 3′ region had no effect on globin gene transcription[109]. These data are in excellent agreement with those described for the adenovirus system. In this context it is interesting that in 15 different mammalian genes the 5′ flanking sequences are enriched in 5′-CpG-3′ dinucleotides, whereas the 3′ regions are rather depleted in these sequences[113]. A high frequency of 5′-CpG-3′ sequences at the left terminus of adenovirus DNA has also been described[4,33]. This 5′-CpG-3′ rich area precedes the E1a region that is important in the regulation of the expression of most other early adenovirus genes[114].

6.2. Methylation of Three 5′-CCGG-3′ Sites in the 5′ Region of the E2a Gene of Adenovirus Type 2 Inhibits its Transcription in Xenopus laevis Oocytes

In Section 4.1, we described perfect inverse correlations between the methylation of all 5′-CCGG-3′ sequences in the Ad2-E2a gene in virus-transformed hamster cells containing viral DNA sequences in an integrated state and the extent to which this gene is expressed (Table 4)[40]. We subsequently showed that in vitro methylation of all fourteen 5′-CCGG-3′ sequences in the cloned E2a gene by prokaryotic *Hpa*II DNA methyltransferase leads to transcriptional inactivation after microinjection into Xenopus laevis oocytes[77,78]. The unmethylated cloned E2a gene is expressed in these cells. We have also reported on the construction of partly methylated clones of the E2a gene[105]. In the promoter (5′)-methylated construct, three 5′-CCGG-3′ sequences at the 5′ end of the subclone were methylated. One of these sites is located 215 base pairs (bp) upstream (bp 26169 of Ad2 DNA), and two sites are located 5 and 23 bp "downstream" from the cap site (bp 25931 and 25949 of Ad2 DNA) of the E2a gene (Fig. 4). This construct was found to be transcriptionally inactive upon microinjection into nuclei of Xenopus laevis oocytes. In the gene (3′)-methylated construct, eleven 5′-CCGG-3′ sequences in the main part of the transcribed gene region were methylated in vitro (Fig. 4). This construct was transcribed in Xenopus laevis oocytes, and at least some of the Ad2-specific RNA synthesized was initiated at the same sites as in Ad2-infected human cells in culture (Fig. 5)[105]. Both mock-methylated constructs were transcribed into Ad2-specific RNA in Xenopus laevis oocytes. Mock methylation experiments were carried out similarly to methylation experiments, except that the methyl donor (SAM) was omitted. These results demonstrate that DNA methylations at or close to the promoter and 5′ end of the E2a

[*] A construct is a highly manipulated plasmid vector into which foreign DNA is often inserted.

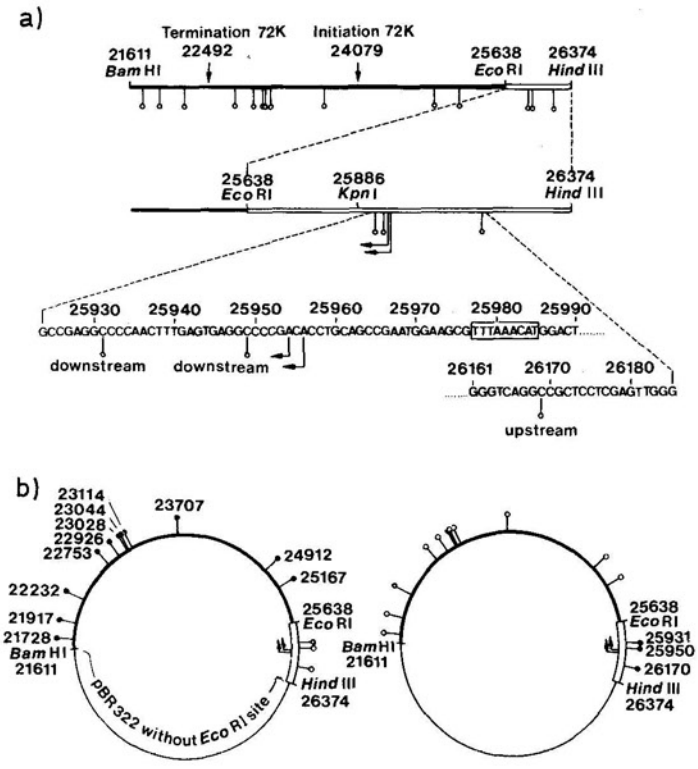


Fig. 4. a) Above: Detailed map of the E2a subclone (*Bam*HI-*Hind*III fragment) of Ad2 of DNA and maps of the promoter (5′)-methylated and gene (3′)-methylated constructs. The DNA-binding protein (DBP = 72 kilodalton protein) is read from right to left. ↓, Initiation and termination sites of translation of the 72 kilodalton protein; ⚲, 5′-CCGG-3′ site; ☤, 5′ C-mCGG-3′ site. The nucleotide sequences of part of the promoter and cap regions (⟵) are shown. The E2a region lacks a canonical TATA (Hogness-Goldberg) signal. The possible equivalent of such a signal has been indicated in a box at ca. 25980. b) Below: Construct which is not methylated (left) or is methylated (right). After injection into Xenopus laevis oozytes, Ad2-specific RNA is found specifically in the first case, but not in the second one. This figure was taken from [105].

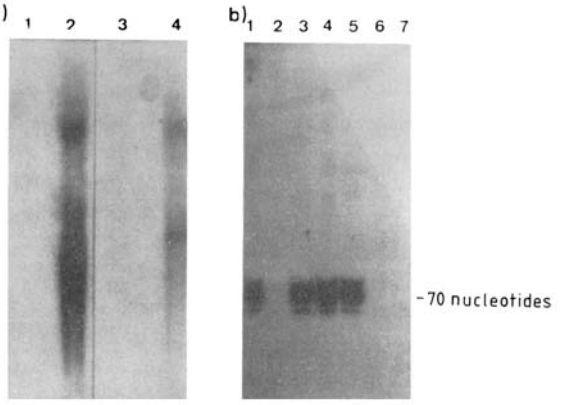


Fig. 5. Methylation of the three 5′-CCGG-3′ sequences in the *Hind*III-*Eco*RI fragment of gene E2a Ad2 DNA (Fig. 4) causes transcriptional inactivation. *Xenopus laevis* oocytes were microinjected with the *Hpa*II methylated (lane 1) or the unmethylated (lane 2) plasmid clone containing the entire *Bam*HI-*Hind*III fragment of gene E2a, the *Eco*RI-*Hind*III promoter (5′)-methylated construct (lane 3), or the *Bam*HI-*Eco*RI gene (3′)-methylated construct (lane 4), as indicated. In each experiment, 5 ng of DNA per oocyte was injected. The total intracellular RNA from 15 oocytes was extracted 24 h after microinjection and fractionated on an 0.8% agarose slab gel containing 2.2 M formaldehyde. The RNA was subsequently transferred to a nitrocellulose filter, and adenovirus type 2-specific RNA sequences were detected by hybridization to ^{32}P-labeled Ad2 DNA followed by autoradiography. b) As indicated below, RNAs were hybridized to the *Kpn*I-*Hind*III fragment of the E2a region of Ad2 DNA (Fig. 4). This fragment was previously 5′-labeled with γ-^{32}P ATP and polynucleotide kinase. The hybrids were treated with S1 nuclease (200 units), separated on a sequencing gel, and identified by autoradiography. Sources of RNA in individual lanes: 1: Ad2-infected human cells, 12 h after inoculation; 2: oocytes injected with the promoter (5′)-methylated construct; 3: oocytes injected with the gene (3′)-methylated construct; 4: oocytes injected with the cloned unmethylated E2a gene; 5: same as lane 4 except that the E2a gene was grown on a dam$^-$ E. coli strain; 6: same as lane 5, except that dam$^-$ plasmid was completely methylated at the 5′-CCGG-3′ sites; 7: RNA from *Zea mays*, negative control. This figure was taken from [105].

gene cause transcriptional inactivation. Perhaps only one methyl group may be adequate for inactivation; in vivo methylation of more than one cytosine may be a form of safeguard or redundancy.

The E2a promoter of Ad2 DNA was also inserted into the pSVO CAT construct and the activity of the unmethylated or the methylated DNA was tested after transfection into human HeLa cells. The results of in vitro promoter methylations were the same in the mammalian system as compared to the amphibian oocyte system: The methylated promoter was inactive, and the unmethylated promoter, active[115].

6.3. Expression of the CAT Gene in Mammalian Cells under the Control of Adenovirus Type 12 Promoters: Effects of Promoter Methylation on Gene Expression

The effect of DNA methylation at specific promoter sites on gene expression was tested by using a sensitive and quantitative assay system. The plasmid pSVO CAT contains the prokaryotic gene chloramphenicol acetyltransferase (CAT) preceded by a *Hind*III site for experimental promoter insertion. Upon insertion into pSVO CAT, the E1a and protein IX gene promoters from adenovirus type 12 DNA were capable of mediating CAT expression upon transfection into mouse cells (Fig. 6, 7)[102].

The CAT-promoting activity of the early simian virus 40 promoter in plasmid pSV2 CAT is insensitive to methylation by *Hpa*II and *Hha*I DNA methyltransferase at the 5′-CCGG-3′ and 5′-GCGC-3′ sequences, respectively, because the promoter lacks such sites. The CAT coding sequence of this plasmid carries four *Hpa*II but no *Hha*I sites. Methylation of the *Hpa*II sites in the coding region does not affect expression. The E1a promoter of Ad12 DNA, comprising the leftmost 525 base pairs of the viral genome, carries two 5′-CCGG-3′ and three 5′-GCGC-3′ sites upstream from the leftmost TATA signal. Methylation of the *Hpa*II or *Hha*I sites incapacitates this promoter in mouse cells (Fig. 7)[102]. Similar results were obtained with the E1a promoter in human HeLa cells and hamster BHK21 cells. Again, methylation inactivated this promoter[127]. The promoter of protein IX gene of Ad12 DNA contains one 5′-CCGG-3′ and one 5′-GCGC-3′ site downstream and two 5′-GCGC-3′ sites >300 base pairs upstream from the TATA motif. The protein IX promoter is not inactivated by methylation of these sites[102]. These data demonstrate that critical 5′ methylations in the promoter region decrease or eliminate transcription; methylations of sites too far upstream and probably sites downstream from the TATA site do not seem to affect expression.

The results discussed in the three preceding sections attest to the methylation sensitivity of two adenovirus pro-

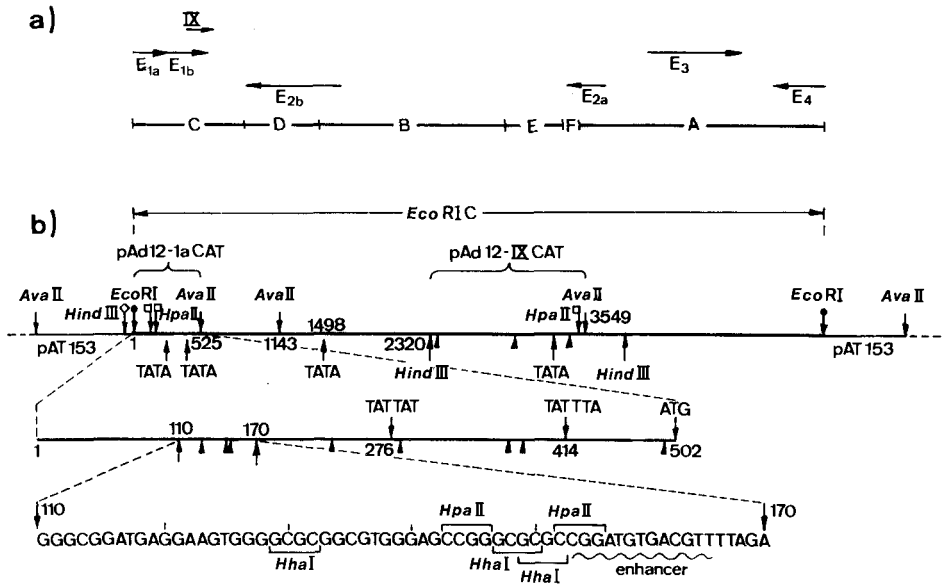


Fig. 6. Map of the Ad12 genome and functional anatomy of its leftmost *Eco*RI-C fragment. a) Functional map of Ad12 DNA [45]. E1a, E1b, E2a, E2b, E3, and E4 designate the early regions of the viral genome; IX designates the location of the protein IX gene of Ad12. Letters refer to DNA fragments on the restriction maps. b) Detailed map of the left-terminal *Eco*RI-C fragment with restriction sites as indicated. Numbers refer to base pairs (bp) counted from the left terminus of viral DNA. TATA (TATTAT, TATTTA) designate the presumptive Hogness-Goldberg boxes. The nucleotide sequence between bp 1 and 502, and 110 and 170, resp., [108] is also included. *Hpa*II (5'-CCGG-3') and *Hha*I (5'-GCGC-3') sites (Δ) are indicated. This figure was taken from [102].

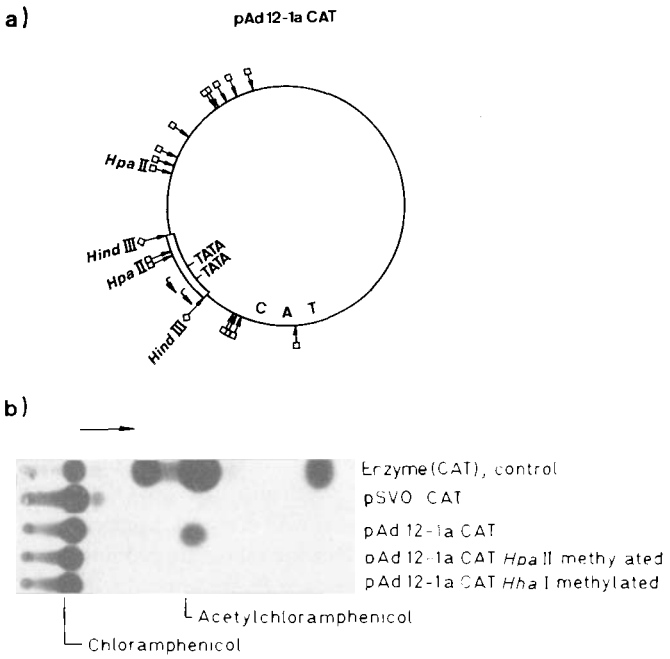


Fig. 7. The E1a promoter of Ad12 DNA mediates CAT expression and is inhibited by methylation. a) Map of the pAd12-1a CAT construct; ⍒ designates 5'-CCGG-3' (*Hpa*II) sites; ⌐→ esignates the approximate TATA positions. b) The pAd12-1a CAT preparation was in vitro methylated by the *Hpa*II or *Hha*I DNA methyltransferase. This figure was taken from [102].

moters and of the globin gene promoter. The data on the viral systems demonstrated that methylation had to occur at specific sites to elicit gene inactivation. One of the viral promoters (E2a of adenovirus type 2) was tested in amphibian oocytes and in mammalian cells; sensitivity toward methylation was the same in both vertebrate systems. Gene activity and its shut-down by site-specific promoter methylation were investigated with the viral gene in the extrachromosomal state[102, 105] or with the globin gene integrated into the recipient cell DNA[109]. In conjunction with the bulk of evidence derived from correlative experiments discussed in Section 4, the data make a strong case for the regulatory function of site-specific promoter methylations in higher eukaryotes.

7. The Occurrence of 5-mC in *Drosophila* is Questionable

The genetics and the molecular biology of *Drosophila* have been studied in considerable detail, and it now represents one of the most thoroughly investigated eukaryotic systems. It is still questionable whether the DNA of Drosophila cells contains any 5-mC. Many of the standard methods have consistently yielded negative results[23, 116, 117] (the modified base also seems to be absent from the DNA of *Saccharomyces cerevisiae*[118]). Recently, it has been claimed that immunological methods have revealed one 5-mC residue per ca. 12500 bases in Drosophila DNA[119]. It is conceivable that even very low levels of 5-mC could exert regulatory functions when positioned in highly strategic points. On the other hand, it has been argued that DNA methylation as a regulatory function is a late addition to the phylogenetic series. Hence, *Drosophila* and other lower eukaryotes—apparently like the prokaryotes—might well be capable of functioning without this regulatory tool. More research will be required to answer these questions, which I consider to be still unresolved.

8. The Possible Role of DNA Methylation in Complex Biological Phenomena: Differentiation, Mutagenesis, and Oncogenesis

It has been convincingly demonstrated that the inactivation of one of the X chromosomes in female cells can—at least in part—be ascribed to site-specific DNA methylation[90, 120]. Genes located on an inactivated X chromosome can be reactivated by growing cells in the presence of the 5-mC analogue, 5-azacytidine. Genes of the reactivated X chromosome could be identified by their products because heterokaryons had been used for the reactivation experiments. The inactive X chromosome was that of human cells in mouse-human hybrid cells. This interesting example emphasizes that complex patterns of differential gene expression or of the shut-off of entire groups of genes can be governed by DNA methylation as a long-term signal for gene inactivation. It is thus plausible that specific methylation patterns have been implicated in affecting other complex biological phenomena.

8.1. Differentiation

Differentiation of cells to functionally highly specific organs as well as the development of pluripotent, undifferentiated cells to organisms with many different highly specialized cell systems can be viewed as the result of a very complicated program of gene activations and inactivations. In highly specialized cells many genes have to be permanently inactivated, and DNA methylation is believed to be at least one of the decisive mechanisms involved in this long-term shut-off of genes. We do not yet understand what mechanisms could account for the apparent specificity of the de novo DNA methylation that would probably have to accompany this inactivation program. Speculations about a specialized arrangement of DNA in chromatin are not satisfactory, since the problem is then transferred to the question of how chromatin arrangements could be generated that are specific enough to attain signal function for DNA methyltransferases. In any event, high priority will have to be given in the future to detailed analyses on DNA methyltransferases.

If specific DNA methylations were a signal for long-term gene inactivation, one would not expect genes to be inactivated by methylation that require to be occasionally reactivated or that have a low level of activity. It is clear that mechanisms other than DNA methylation must be involved in gene inactivation, e.g. specific proteins binding to regulatory DNA sequences. DNA methylations may only modulate these protein-DNA interactions. For example, certain genes encoding essential functions may have to be occasionally reactivated and should not be shut off permanently. A further interesting example are genes that can be activated by steroid hormones; these genes are usually not methylated. For other genes we do not yet sufficiently understand their temporal activity patterns to predict the extent of DNA methylation. It is assumed that highly specialized genes remain active only in certain organs of an animal. Can one, however, be certain that these specific messages are not also occasionally produced in other cells of the organism? If such necessities arose, DNA methylation would not be the signal of choice to inactivate this set of genes. With this reasoning, a scheme can be developed that operationally subdivides genes into at least three classes[17]:

1) Permanently inactivated genes
2) Inactive genes that are occasionally reactivated
3) Active genes

This classification will undoubtedly have to be refined as an improved understanding of differential gene activities emerges. In this simple scheme, DNA methylation would be expected to be a signal of inactivation in class I genes only.

8.2. Mutagenesis

Reports have appeared[94] which demonstrate that the presumptive inactivation of a gene, the inactivation of the thymidine kinase (tk) gene in "tk^- mutants", is due to site-specific DNA methylation. The "mutation" in that particular case could be reversed by growing the "mutant" cells in the presence of 5-azacytidine. As explained in Section 4.3, this analogue inhibits the maintenance DNA-methyltransferases and hence leads to a decrease in DNA methylation and to the induction of previously inactivated genes. This interesting experiment points out the necessity of reexamining the definition and concept of mutation.

8.3. Malignant Tumors

There is an increasing amount of evidence that the DNA in many tumors is strongly hypomethylated compared to the DNA in normal cells[121]. This hypomethylation has been observed for DNA in general[122], as well as for specific genes[123]. Cancer cells differ from normal cells in many respects, certainly by altered patterns of expression of many genes, not only of the fashionable oncogenes[124, 125]. These two findings—decreased levels of DNA methylation and altered patterns of gene expression in cancer cells—are fully compatible with each other. The bulk of the work in the future will have to concentrate on demonstrating specificities in gene activation or inactivation and in differentiating between cause and effect. I caution the reader against drawing hasty conclusions. Hypomethylation has *not* been shown to be causally related to malignant transformation; it could be one of the many epiphenomena that have in the past sometimes been mistaken for etiologic leads. Nevertheless, the search for specificities in changes in methylation patterns in cancer cells will continue.

In conclusion, I should like to describe an example from our own work on the adenovirus system[37, 38, 126]. The analysis of methylation patterns of adenovirus type 12 DNA in virus-induced tumors revealed that in tumor cell DNA the integrated viral DNA sequences were still hypomethylated although viral DNA was not extensively expressed. Upon explantation of tumor cells into culture, the extent of methylation of viral DNA increased gradually with continued passage of the tumor cells in culture. This increase was not random but followed a certain pattern leading eventually to the hypermethylation of the integrated late viral genes[38]. Similar observations were made when the cells

were subcloned at an early stage after explantation from the tumor. At present, it is not understood what factors regulate the establishment of organized patterns of methylation of the viral genome after insertion into the host genome. Concomitant with, but perhaps only temporally related to the increase in viral DNA methylation, the viral genome had a tendency to be excised again and lost from the host cells during early passages after explantation[38].

9. Outlook

As is frequently the case in research, investigations on the biological role of DNA methylation have raised more questions than they have answered. Work on DNA methylation has developed into a rapidly expanding field. Among the most important issues under investigation in several laboratories are the following:

1) Promoter methylations at specific sites and sequences, and their effect on gene activity,
2) Significance and mode of generation of complex patterns of DNA methylation, particularly in the non-promoter parts of genes,
3) Specificity and regulation of activity of DNA methyltransferases in eukaryotic cells,
4) The problem of active demethylation,
5) Application of the genomic sequencing technique[26] to establish precise patterns of DNA methylation, particularly in inactivated promoter sequences,
6) Mechanism and biological significance of shifts in patterns of methylation,
7) Binding of (specific?) proteins to methylated DNA,
8) The role of DNA methylation in the formation of chromatin,
9) The function of DNA methylation in complex biological processes.

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The Homoaldol Reaction, or How to Overcome Problems of Regio- and Stereo-selectivity**

New Synthetic Methods (50)

By Dieter Hoppe*

Dedicated to Professor Wolfgang Lüttke on the occasion of his 65th birthday

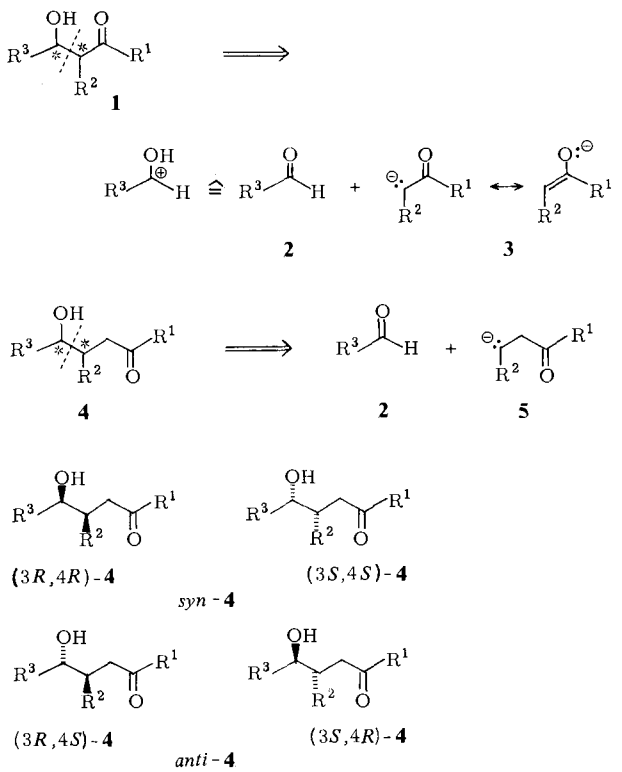
Even today, there are conspicuous gaps in the register of organic synthetic methods. Thus, numerous types of homoenolate reagents are listed; yet no generally applicable method for the homologue of the aldol addition, viz. the homoaldol addition, is to be found. The methods documented up to 1980 offer only singular solutions, and, moreover, are not stereoselective. The present article gives an overview of the existing possibilities and then describes how the gap can be closed by using a new class of homoenolate reagents: 2-alkenyl esters of *N,N*-diisopropylcarbamic acid are lithiated and the resulting allyllithium compounds tailored to high regio- and diastereoselectivity in addition reactions to the carbonyl group via metal exchange. Altogether, the homoaldol reactions now offer a general and reliable, highly stereoselective entry to γ-hydroxycarbonyl compounds, whereby the C(β)–C(γ) bond is formed. Furthermore, it is demonstrated how problems associated with the application of allyl anions as synthetic reagents can be solved today.

1. Introduction

Nowadays, in the synthesis of an organic compound it generally does not suffice to merely build up the carbon skeleton with a given constitution, i.e. with the correct sequence of atoms. Rather, the target molecule is desired as a pure diastereomer, at least as a racemate (i.e. with a particular relative configuration), or even in enantiomerically pure form (i.e. with a particular absolute configuration). A further difficulty is brought about by the complexity of many target molecules; they—and consequently also the many precursors and intermediates—often carry several functional groups of similar reactivity, of which only one may be transformed in each reaction step. Hence, selective methods and reagents are required, and all the more so the more complex the nature of the target molecule. In order to keep the number of steps small (and thus the overall yield high), each synthetic step should yield not only the correct constitution, but also the correct configuration.

The progress made over the past few years has largely been due to a mastering of these problems as far as standard synthetic building blocks are concerned. The aldol addition and its numerous close and distant relatives are striking examples[1]. For example, several good preparative methods are available for constructing β-hydroxycarbonyl compounds **1** (R^1 = H, aryl, or OH) from the synthons **2** and **3**, which were ascertained by the retrosynthetic analysis[2] of **1** (Scheme 1). They offer specific access to both diastereomers of **1** either as racemate or even in enantiomerically pure form; often, there is a choice of several methods of varying efficiency and simplicity.

Which methods are available for the diastereoselective synthesis of a *syn* or *anti*[4–6] γ-hydroxycarbonyl compound **4**, e.g., a precursor of one of the numerous naturally occurring γ-lactones (Scheme 1)? **4** is homologous to the aldol **1**. From experience gained with the aldol addition, a bond cleavage between the β- and γ-C's to give the aldehyde **2** and the homoenolate anion **5** would seem very tempting; it calls for a "homoaldol addition"[7]. An important consideration here is that the newly created centers of asymmetry, formed upon fusion of two prochiral centers, should be easily controllable.



Scheme 1. Retrosynthesis of aldols **1** and homoaldols **4**. The CIP-descriptors [3] are valid provided R^2 and R^3 = *n*-alkyl. Variation of R^1 has no influence.

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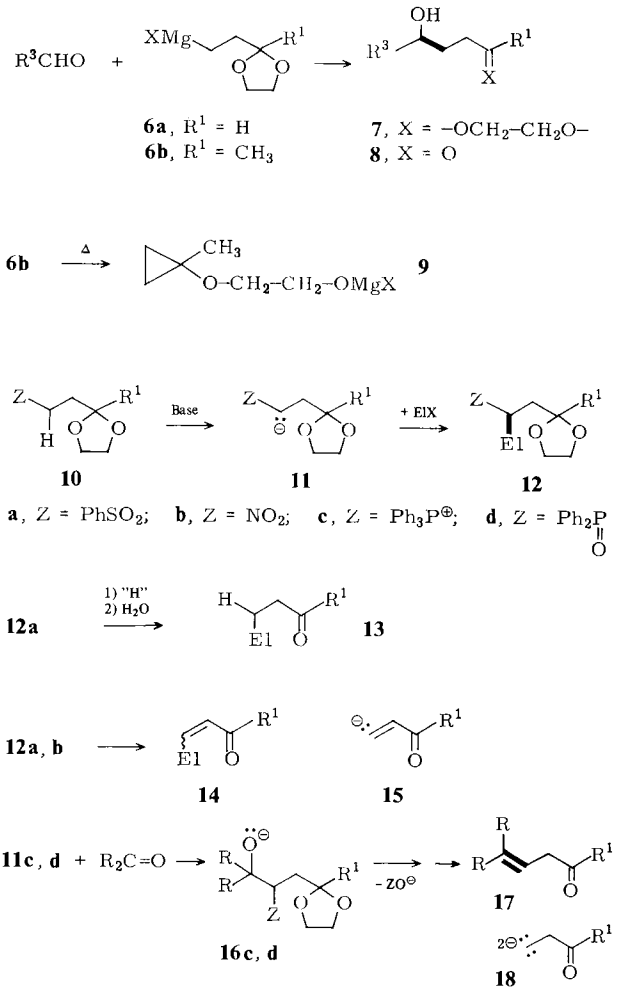
The problem is now to find a reagent[8] for the homoenolate ion **5**, viz. a d^3-synthon[9], which adds diastereoselectively to aldehydes. A literature search up to the year 1981 fails to bring any useful method to light. The difficulty is obvious: the synthon **5** has suffered "umpolung"[9]. In contrast to the enolates, where mesomeric stabilization is the driving force for their formation, the carbonyl group in **5** does not contribute to a stabilization of the negative charge. Furthermore, in enolates **3** the carbonyl group is protected by resonance against nucleophilic attack. Thus, the second problem is apparent: even if it were possible to generate a homoenolate by methods other than deprotonation (e.g. halogen-metal exchange), its carbonyl group and the neighboring hydrogen atoms would be susceptible to side reactions such as transprotonation to form the enolate or uncontrolled additions. Although homoenolates **5** have been detected as short-lived intermediates via deuteration in the β-deprotonation of nonenolizable ketones[8c] under drastic conditions, or in the ring opening of cyclopropanolates[8c], the concentrations of **5** so obtainable are too low for a preparative exploitation.

2. Homoenolate Reagents with Blocked Carbonyl Group—The Defensive Strategy

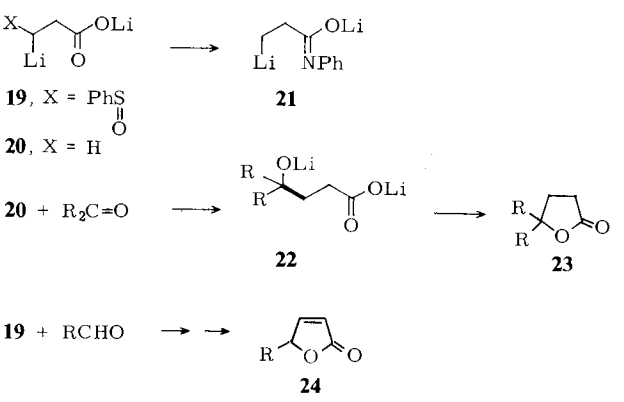
As a consequence of the above, at least the electrophilic carbonyl group must be protected in homoenolate reagents. This defensive strategy was probably used for the first time in 1969 by *Büchi* and *Wüest*[10], who added the Grignard reagent **6a** (generated from the β-bromoacetal) to an aldehyde and subsequently removed the protecting group in the adduct **7** by hydrolysis (Scheme 2). Although **6a**, **6b**, and similar magnesium[11], copper[12], or lithium compounds[13] are more frequently used for propanal- and 2-butanone-d^3-reagents, this solution is apparently not generally applicable, for it has not yet been described for β-alkylated homoenolates. The observations made by *Feugeas*[14] indicate the reason: there is a danger of a 1,3-cycloelimination in **6b** to give the cyclopropyl ether **9**. This tendency should increase with the degree of alkylation.

"Homoenolate ions" of the type **11a** are directly accessible from the acetals **10a** by deprotonation when a stabilizing arylsulfonyl group is present in position 3. However, this simplification in their generation must be paid for at the cost of a further reaction step, namely the reductive removal of the activating group. Some further d^3-reagents have been prepared according to the general principle presented in **11**, i.e. acetalized carbonyl group and strongly electron attracting β-substituent Z. Examples are nitroacetals **11b**[16], phosphonium compounds **11c**[17], and phosphane oxides **11d**[18]. Liberation of the carbonyl group in the adducts **12a** and **b** is followed by an elimination to the α,β-unsaturated carbonyl compound **14**, or else olefins **17** are formed from Wittig intermediates **16c**, **d**. Therefore, these reagents correspond to β-acylvinyl anions **15**[19] or β-carbonyl dianions **18**.

The carbonyl group and neighboring protons in carboxylic acid derivatives can also be deactivated "electronically" by carboxylate resonance (Scheme 3): first one equivalent of base is used to generate a carboxylate; the β-proton activated by the presence of the phenylsulfinyl group is now removed with lithium diisopropylamide to give the dianion **19**[20,21]. **19** has proven of value in the synthesis of 2-buten-4-olides **24**. Dilithium propionate **20**[22], as well as the anilide **21** [23] are also obtainable by way of a halogen or tin/lithium exchange reaction. They were used in the synthesis of γ-lactones **23**.



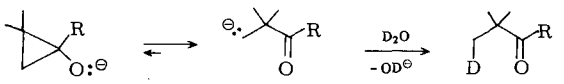
Scheme 2. Acetals as homoenolate reagents. The newly formed bonds are shown in bold print.



Scheme 3. Mesomerically protected homoenolates.

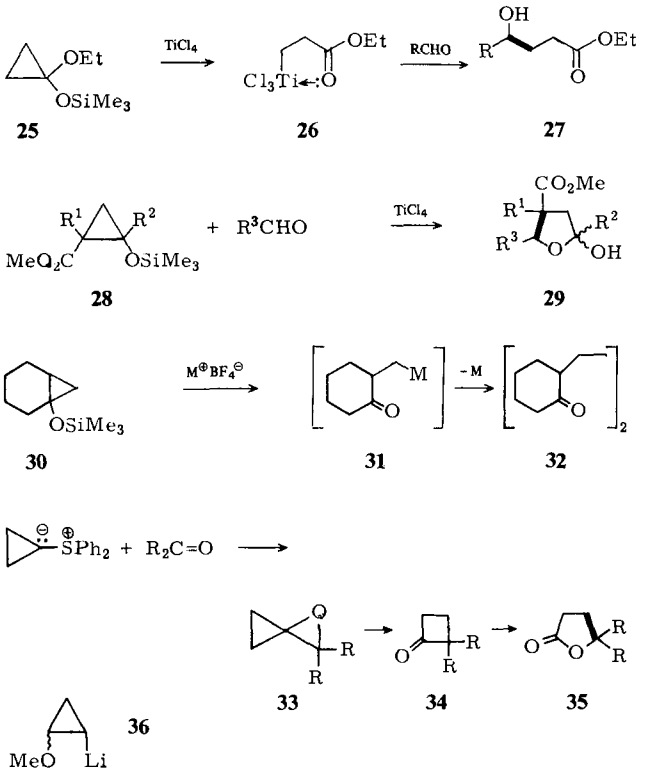
3. The Cyclopropane Route

Several studies have shown[8c] that the ring opening of cyclopropanolates in protic media occurs via β-enolates; yet the carbanion concentrations so obtainable are too low to allow their trapping by electrophiles of lower reactivity than $H^{\oplus}$ or $D^{\oplus}$. However, according to *Kuwajima* et al.[24],



hydroxyalkylation of acetals such as **25** with aldehydes to give γ-hydroxy esters **27** can be carried out in the presence of equimolar amounts of titanium tetrachloride (Scheme 4); the titanium homoenolate **26** has been characterized as an isolable intermediate[24b]. The analogous trichlorostannyl compound obtained with tin tetrachloride[25] has been characterized by X-ray analysis. *Reissig* has recently shown that 2-silyloxycyclopropanecarboxylic acid esters **28** react analogously to give the γ-lactols **29** with aldehydes[26]; thus, this reagent is more like a γ-oxoenolate and can only formally be regarded as a homoenolate equivalent. The "metal homoenolates" **31** have been proposed as intermediates in the oxidative dimerization of cyclopropyl trimethylsilyl ethers such as **30** to 1,6-diketones **32** in the presence of silver or copper tetrafluoroborate recently reported by *Murai* et al.[27]. Stable "mercury homoenolates"[28] (M = AcOHg in **31**) obtained with mercury(II) acetate are used by the *Giese* group[29] as radical precursors, e.g. in the synthesis of diketones of the type **32**.

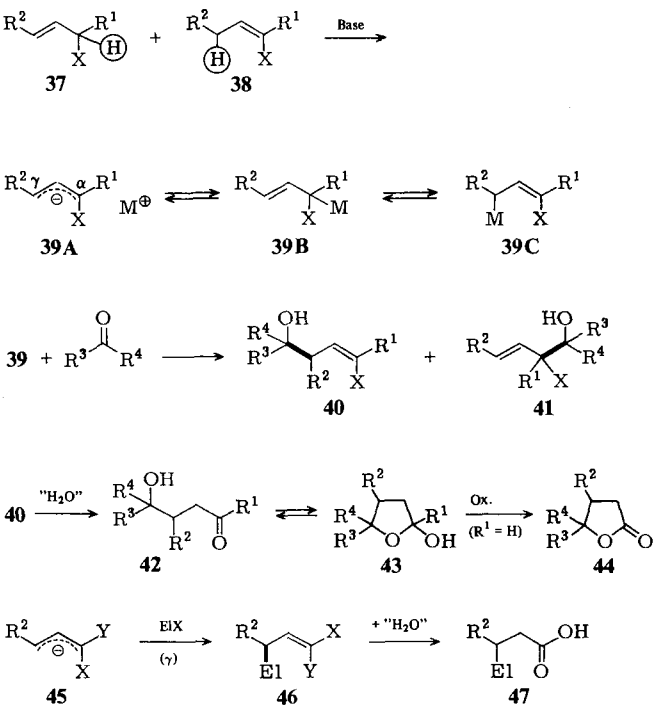
The ring strain in cyclopropanes has also been exploited in indirect reaction sequences to yield homoaldol derivatives. Thus, according to *Trost* et al.[30], the addition of a diphenylsulfonium cyclopropanide to a ketone gives the spirooxirane **33** which after rearrangement to the cyclobutanone **34** is subjected to a Baeyer-Villiger oxidation to give the γ-lactone **35**. The overall outcome of this sequence is only the addition of the propionic acid d^3-synthon to a carbonyl compound. This solution should be less attractive for the introduction of alkyl substituted homoenolate units because of problems with regioselectivity in the rearrangement step. 2-Methyloxycyclopropyllithium **36** has been used by *Corey*[31] since 1975 as a special homoenolate reagent.



Scheme 4. Cyclopropanes as homoenolate precursors.

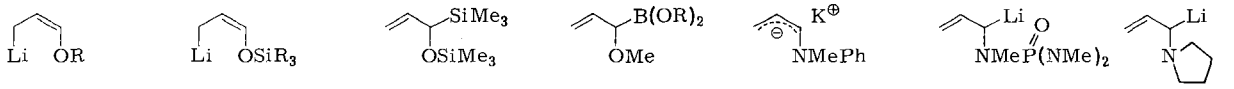
4. The Offensive Strategy— The Allyl Anion Route with Many Problems

The reagents described in Sections 2 and 3 offer solutions only for the parent compounds and a few special cases. The "allyl anion strategy" is found to be more versatile. This strategy was first used by *Biellmann* et al.[32,33] and *Corey* et al.[34], albeit with other objectives, and since 1972 by *Ahlbrecht* et al.[8a,35] from the point of view of homoenolate reagents. Here, the necessary functionality in position 1 is used offensively to build up an allylic resonance; occasionally, also the hetero substituent X (Schemes 5 and 6) is used to stabilize the allyl anion **39**. Generally, the precursor is the allylic compound **37** (or more rarely the less acidic vinylic isomer **38**[8a]), which is deprotonated with the aid of strong bases. The reaction between **39** and an aldehyde or ketone gives the regioisomeric adducts **40** and **41**. Provided the substituent X is attached through an electronegative atom (O, N, or S), the 4-hydroxyalkene **40** affords the homoaldol **42** on hydrolysis; the latter is in tautomeric equilibrium with the γ-lactol **43**.

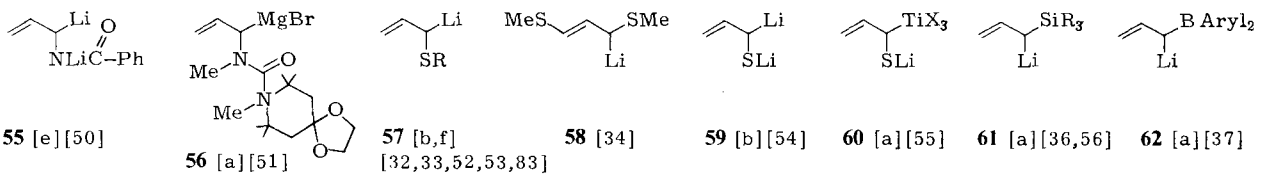


Scheme 5. General Scheme for homoaldol reactions with allylmetal compounds. A particular stereochemical outcome is not implied at this stage.

Propanal-d^3-reagents:

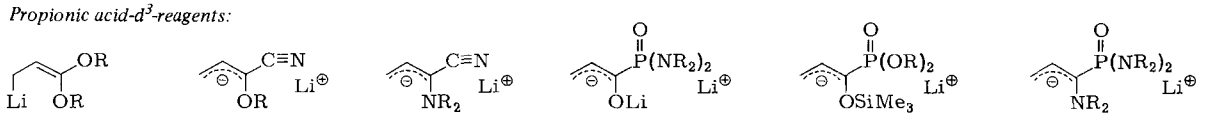


48 [d][38-41] **49** [d][42-44] **50** [e][45] **51** [a][46] **52** [c][47] **53** [e][48] **54** [c][49]



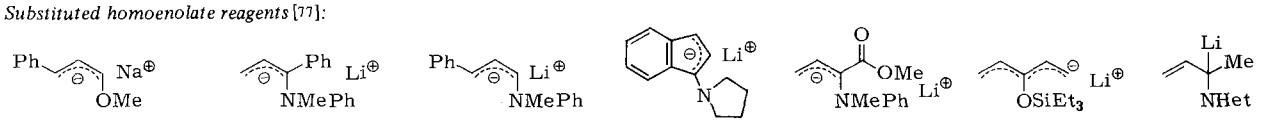
55 [e][50] **56** [a][51] **57** [b,f] [32,33,52,53,83] **58** [34] **59** [b][54] **60** [a][55] **61** [a][36,56] **62** [a][37]

Propionic acid-d^3-reagents:

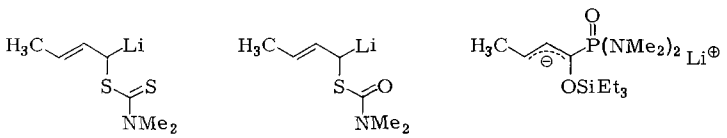


63 [e][57] **64** [a-d][58,59] **65** [a-d][60,61] **66** [a,b][62] **67** [a,b][63] **68** [a,b][64]

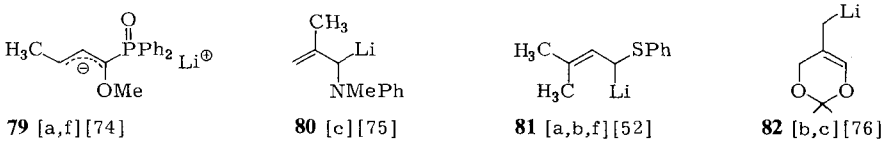
Substituted homoenolate reagents [77]:



69 [e][65] **70** [a][35] **71** [a][66] **72** [e][67] **73** [a][68] **74** [a][69] **75** [a,g][70]



76 [a,f][71] **77** [a,f][72] **78** [a][73]



79 [a,f][74] **80** [c][75] **81** [a,b,f][52] **82** [b,c][76]

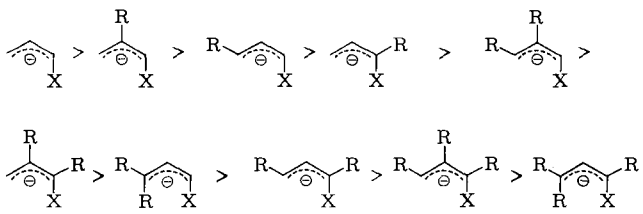
Scheme 6. Selected homoenolate reagents on the basis of allyl anions and the regioselectivity (*rs*) of their addition to carbonyl compounds. Here, regioselectivity (*rs*) means the amount (in %) of the regioisomer concerned. [a] High γ-regioselectivity, > 90% *rs*. [b] Medium γ-selectivity, > 65% *rs*. [c] No γ-selectivity, 60—40% *rs*. [d] α-Selective carbonyl addition. [e] Selectivity not known. [f] The deblocking of the γ-adducts has not been described. [g] NHet = 9-carbazolyl.

If the γ-adduct **40** carries electropositive residues X (e.g. trialkylsilyl[36], diarylboryl[37]) an additional oxidation step is necessary.

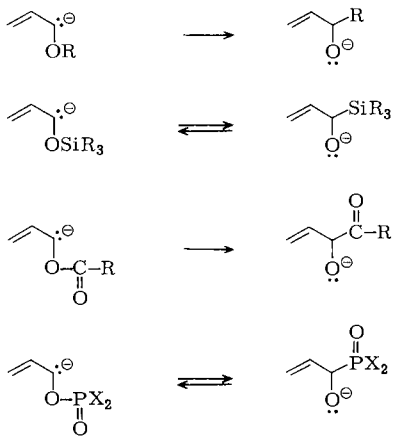
Further oxidation of the aldehyde derivatives **42** and **43** leads to acids which are mostly isolated as γ-lactones **44**. 1,1-Bisheterosubstituted allyl anions **45** (Y = e.g. phosphoryl, groups derived therefrom, and also CN, Scheme 6) are more direct, although not always more useful preparative solutions, because an acid, **47**, is directly obtained by hydrolysis of the γ-adducts **46** (Scheme 5).

The use of allyl anions as homoenolate reagents also brings new problems, however.

Stability and range of application: The stability of anions **39** is drastically reduced by alkyl groups R^1 and R^2, particularly in the electron rich α- and γ-positions; that is, increasing alkylation makes it more difficult to generate allyl anions, and they become more prone to decomposition (Scheme 7). 1-Oxyallyl anions in particular are prone to rearrangement, such as the Wittig[78] and Brook[43-45,79] rearrangements as well as acyl[80] and phosphoryl[62] migrations (Scheme 8). However, the reversibility of the Brook rearrangement can also be exploited for the preparation of anions **49** in low stationary concentrations from 1-trialkylsilyl-2-alkenolates[43-45]. In contrast, electron-withdrawing substituents R^1 and R^2 contribute to the stabilization of allyl anions of the type **39** and it is no surprise, therefore, that many substituted homoenolate reagents carry phenyl, vinyl, or carbonyl groups (Scheme 6).



Scheme 7. Hindrance of the deprotonation of allylic compounds with increasing degree of alkylation. X is constant, R = alkyl (e.g. CH_3).



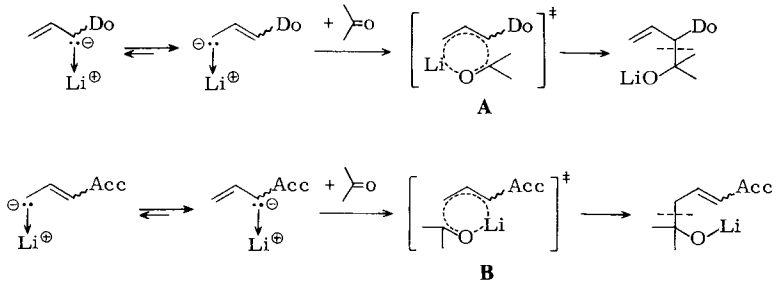
Scheme 8. Rearrangements of 1-oxyallyl anions.

Regioselectivity: The isomer ratio **40/41** (γ/α adduct) of the kinetically controlled electrophilic substitution of ambident anions[81] such as **39** is influenced in a complicated manner by substituents, by counterions, by the solvent, and by the electrophile[91]. Often a reversal of the regioselectivity accompanies a change from alkyl halides to carbonyl compounds. Thus, lithiated 2-propenyl ethers **48** or **49**—investigated since 1974 by *Evans*[38], *Schlosser*[39], *Still*[42], and several other groups[40,41,43–45]—are selectively alkylated in the γ-position, but hydroxyalkylation takes place selectively in the α-position. This tendency is enhanced by metal exchange[38,41,42] with magnesium bromide, zinc chloride, or diethylaluminum chloride[82]. The opposite trend applies in the case of the corresponding metalated thioethers **57**[32,33,41,53,83]. Since the perturbation of the allylic system due to the substituents R^1 and R^2 in **39** is of the same order of magnitude as that due to the substituents X, the regioselectivities obtained for the parent systems (R^1 and R^2=H) seldom pertain to substituted derivatives. A rule of thumb, unshaken by many exceptions, whereby the steric situation, influence of solvent, and bonding of the cations are left out of consideration, can be formulated as follows:

> An introduction of donor substituents[81] (including alkyl groups) in "allyl anions", where M=Li, shifts the carbonyl attack in the direction of α-selectivity. In contrast, acceptor substituents cause increased γ-selectivity (Scheme 9). These influences are reversed in alkylations and silylations[81].

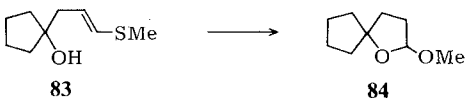
The selectivity rules for addition to the carbonyl group are most closely obeyed for less stabilized allylic compounds in nonpolar media because here the formation of tight ion pairs is particularly pronounced (Scheme 9).

A high degree of γ-selective carbonyl addition (Scheme 6) is shown, for example, by the pentadienyl derivative **74** of *Oppolzer* et al.[69], the 1-phenyl compound **70** of *Ahlbrecht* et al.[8a,35], the 3-methylated phosphoric amide **78** of *Evans* et al.[73], and the prenyl derivative **81**[52]. The ion pairing, determined by the anion polarization[81], can, however, be reversed by chelation using good complexing ligands and appropriate cations. The magnesium-urea derivative **56** reported by *Seebach* et al.[51] is hydroxyalkylated with a high degree of γ-selectivity.



Scheme 9. Model concept for guiding the regiochemistry of carbonyl additions through the position of the counterion. Do=donor-, Acc=acceptor-substituent. **A**, **B**: Transition states.

Deblocking: Among the reagents indicated in Scheme 6 the 1-thio-substituted allyl anions of the types **57**, **76**, and **77** tolerate the highest number of attached alkyl groups. Yet, a mild deblocking of the resulting thioenol derivatives of the type **40** (X=SR') is difficult or has even been unsuccessful so far[84]. Thus, the methanolysis of the cyclopentanone adduct **83** leading to the spiroacetal **84** requires the addition of 3 molar equivalents of mercury(II) chloride[55b]. The acid-catalyzed hydrolysis[8a] of enamines (X=NR_2 in **40**) and enol ethers[84] (X=OR in **40**) to aldehydes and ketones is, however, in general easy to perform.



83 **84**

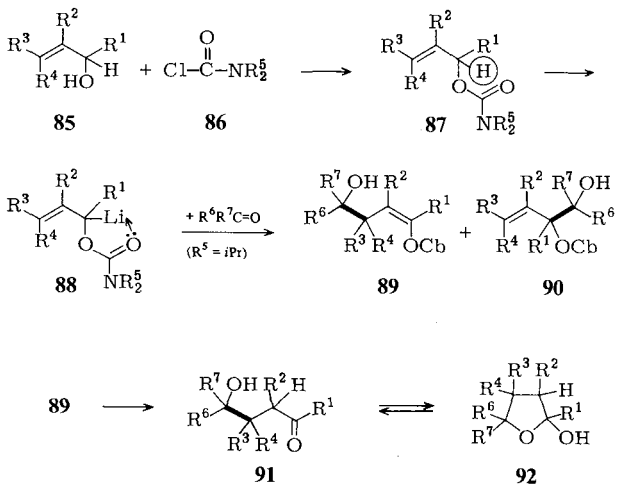
5. The Solution: Metalated Allyl Carbamates

The problems described above lead to the following demands on any new class of generally applicable reagents for the homoaldol reaction:

- Reliable γ-selectivity in the carbonyl additions, independent of the substituent pattern.
- General, facile access.
- Mild and selective deblocking of the adducts.
- Option on stereoselective versions.

When we became aware of the problem in 1979[85], no type of reagent was known which would satisfy all requirements. However, the ground had been prepared for a satisfactory solution. *A. I. Meyers, Beak,* and many others had demonstrated the importance of the long known "chelate effect"[87] for directed lithiations. The investigations on allylic boranes by *R. W. Hoffmann*[88a] had made it clear that, in nonpolar media, the regiochemistry of the addition to the carbonyl group is controlled to a large extent by the position of the "cation" (which directs the incoming carbonyl group to the γ-position in the pericyclic process with allylic inversion). The sequence is similar to the isoelectronic aldol addition[1] and hence uniform prochirality in the starting material **39** is the key to high diastereoselectivity.

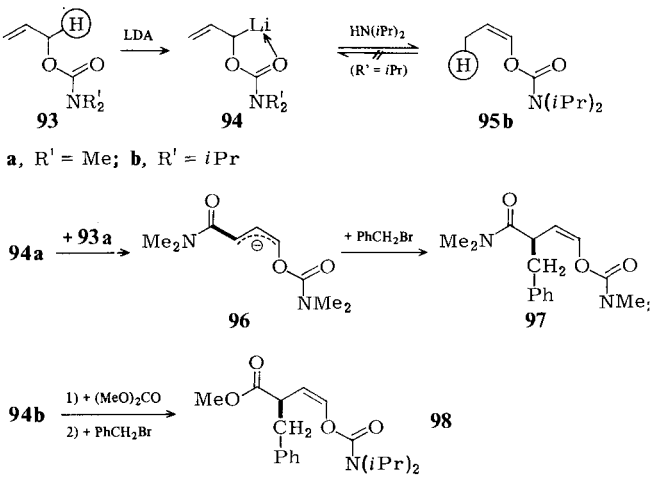
Conclusion: The "cation" in the allylmetal compound **39** has to be located in the 1-position (see **39B**). Therefore, the group X must actively participate in locating the cation there. Increased thermodynamic stability of the species **39** and a high kinetic acidity of the precursor **37** would be "additional bonuses", as an interaction between the residue X and the cation should take place already in the transition state and lower the energy of deprotonation; both of the aforementioned effects are essential for a wide range of applicability. Which groups X are capable of providing all this? Since we have been concerned with metalated thiocarbamic acid esters[72,89], e.g. of the type **77**, *N,N*-dialkylcarbamoyloxy groups appeared to be promising candidates (Scheme 10). 2-Alkenyl esters **87** of carbamic acid are easily and generally accessible from allyl alcohols **85** and chlorides **86** under the action of pyridine[90] or other bases[91,72b], whereby the regio- and stereochemistry of the educt are left unaltered[92]. Since γ-addition of aldehydes and ketones to lithium compound **88** leads to the enol esters **89**, no problems are expected in the solvolytic deblocking to the homoaldols **91**.



Scheme 10. Homoaldol reaction with allyl carbamates. Reaction **87**→**88** with *n*-butyllithium/tetramethylethylenediamine (TMEDA) in tetrahydrofuran (THF)/hexane, −78°C (standard conditions). Cb = *N,N*-dialkylcarbamoyl; unless otherwise stated, Cb = C(O)–N(*i*Pr)$_2$.

As a first test, 2-propenyl *N,N*-dimethylcarbamate **93a** was stirred with lithium diisopropylamide (LDA) in THF/hexane at −78°C and the mixture treated with benzyl bromide in order to detect any anions formed. The 3-butenoic acid amide with *Z*-configuration **97**[93,72b] was isolated in 40% yield (based on LDA). Thus, it was ascertained that the allyllithium compound **94a** is an intermediate, but it rapidly reacts with the ester **93a** with transposition of the dimethylcarbamoyl group and, after a second deprotonation, forms the vinylogous amide enolate **96**. Finally, the latter is benzylated in the position alpha to the acceptor[81] (Scheme 11).

This "self-condensation" is decelerated by bulky *N*-substituents; the *N,N*-diisopropyl derivative **93b** merely isomerizes under the reaction conditions mentioned[93,72b] to give the (*Z*)-1-propenyl carbamate **95b**. The intermediary anion **94b** is trapped in situ with dimethyl carbonate (which is inert to LDA below −70°C!) and, after benzylation, affords the (*Z*)-butenoic ester **98** together with smaller amounts of the α-adduct. Thus, the procedure offers a simple and flexible access to masked 4-oxoesters[93].



Scheme 11. *In situ* generation and trapping of lithium compounds **94**.

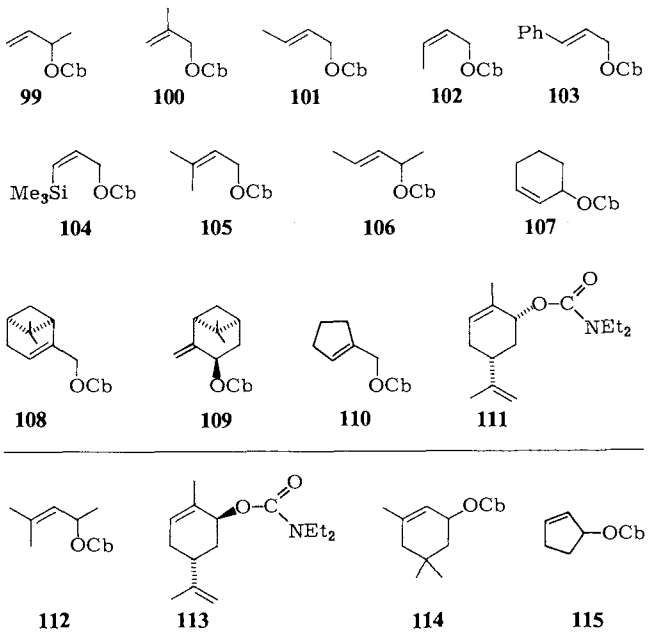
Accordingly, the basicity of LDA suffices for the generation of low concentrations of **94b**, but in the absence of a reactive electrophile this compound is irreversibly protonated by diisopropylamine, giving the more stable enolic carbamate **95b**. According to *Hine*[94], the energy difference ΔG° between the two isomers **93b** and **95b** is estimated as ca. 3 kcal/mol, corresponding to less than 3 pK_a units at −78°C. Hence, the ion pair acidity of the allyl carbamate **93b** in THF should be slightly less than that of diisopropylamine (p$K_a \approx 36$)[95].

n-Butyllithium in the presence of 1.0–1.1 molar equivalents of the complexing agent tetramethylethylenediamine (TMEDA)[96] in ether/hexane or even pure hydrocarbons at −78°C to −70°C proves to be the best reagent for the complete deprotonation of *N,N*-diisopropyl carbamates **87** (R^5 = *i*Pr). No products derived from an addition of butyllithium to the sterically blocked carbonyl group are formed.

As shown by silylation[72b], the extent of lithiation of the parent compound **93b** is already at least 88% after 5 min (see also Scheme 14). Introduction of a methyl group in the α, β, or γ positions in the carbamates **99**–**102** (Scheme 12) leads to only a slight decrease in kinetic acidity (complete lithiation in $t = 15$–30 min[72b]). The system even allows the presence of two alkyl groups in any desired positions without difficulty, as shown by the carbamates **105** ($t = 30$ min) and **106** ($t = 3.5$ h). However, the limit is exceeded in the case of the 1,3,3-trimethyl derivative **112**, which is inert toward *n*-butyllithium[97]. The allylic unit may also be part of a six-membered ring (as in **107** or **111**), or parts thereof may be comprised in five- or six-membered rings as in **108**–**110** ($t = 3$–5 h)[97]. Other ring sizes have not, so far, been investigated. Surprisingly, the 2-cyclopentenyl and the *trans-p*-menthadienyl carbamates **115** and **113** are not lithiated under standard conditions[97]. Possibly, conformational effects lower the kinetic acidity of these carbamates because the C–H bond to be

broken experiences an unfavorable "dihedral" angle with the π system.

As expected, a 3-phenyl substituent increases the acidity considerably: **103** is completely deprotonated in less than 1 min by LDA[72b]. The investigation of hetero-substituted analogs such as the 3-trimethylsilyl derivative **104** has just begun[98].



99 **100** **101** **102** **103**

104 **105** **106** **107**

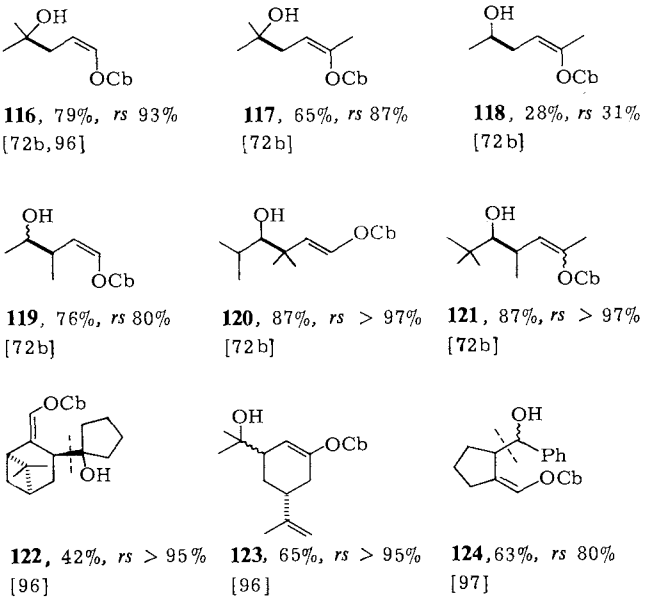
108 **109** **110** **111**

112 **113** **114** **115**

Scheme 12. Limits of the lithiation of 2-alkenyl carbamates **87** under standard conditions (see text). **112**–**115** are not lithiated.

All in all, the lithiation of allyl carbamates provides a general entry to 1-oxyallyl anions with a structural variety previously inaccessible, and thus also to potential homoenolate reagents.

The reaction[96,72b] between solutions of allyllithium compounds of the type **88** and aldehydes or ketones is rapid at $-78\,^{\circ}C$, giving mainly γ-hydroxyenolcarbamates **89** together with varying amounts of the α-adducts **90** (Scheme 10). Some representative examples which also illustrate the limits of the lithium variants are given in Scheme 13.



116, 79%, *rs* 93% [72b,96]

117, 65%, *rs* 87% [72b]

118, 28%, *rs* 31% [72b]

119, 76%, *rs* 80% [72b]

120, 87%, *rs* > 97% [72b]

121, 87%, *rs* > 97% [72b]

122, 42%, *rs* > 95% [96]

123, 65%, *rs* > 95% [96]

124, 63%, *rs* 80% [97]

Scheme 13. Examples of the addition of **88** to aldehydes and ketones. The respective yields and regioselectivity are given; in the case of **116**–**124** % *rs* refers to the amount of the γ-adduct in the regioisomer mixture.

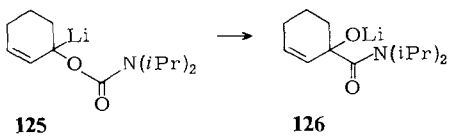
The γ-selectivity of the carbonyl addition increases with increasing 3-substitution and with decreasing 1-substitution in the allyl anion **88** and also with decreasing reactivity of the carbonyl group in the reaction partner. Ketones are better than aldehydes. Both factors favor a cyclic transition state of the type **B** (Scheme 9) and disfavor other alternatives. The second parameter is the most important: The addition reactions of the allyl and 1-methylallyl derivatives **93b** and **99** to acetone to give **116** and **117**, respectively, have similar regioselectivities[72b] (Scheme 13), whereas replacement of acetone by acetaldehyde leads to a loss of γ-selectivity in the product **118**[99].

6. Structure and Properties of Lithiated Carbamates

Although as yet no X-ray structure determination is available, the reactivity of the lithium compounds **88** allows informed speculation about their structure.

a) The lithiation of the esters **87** succeeds only in the presence of at least one molar equivalent of a bidentate complexing agent such as TMEDA; this being satisfied, the reaction is fast even in hydrocarbon solvents[100].

b) The lithium compounds **88** are persistent in nonpolar solvents, at least below $-70\,^{\circ}C$. In donating solvents like THF or 1,2-dimethoxyethane, however, they rearrange to salts of α-hydroxyamides such as **126**[97]; this is also the case when lithium is exchanged for potassium.



125 **126**

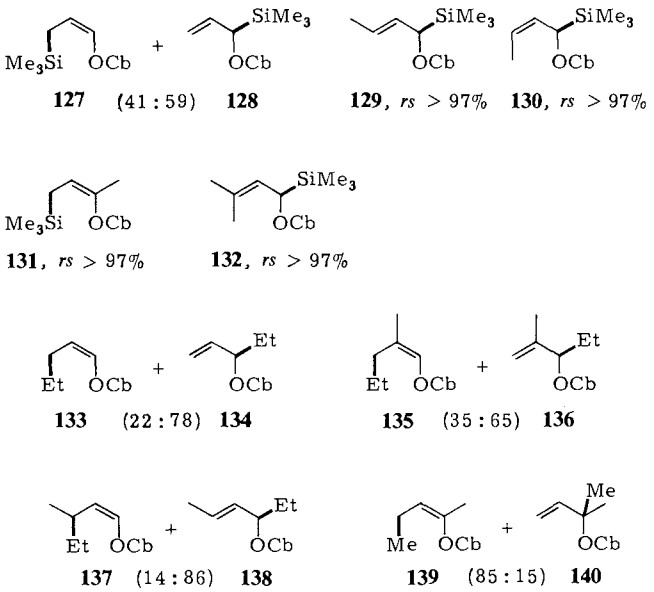
c) As long as the allylic system **88** does not carry a 3-*cis*-substituent and the molecular framework does not enforce (1*E*)-configuration (e.g. in cycloalkenyl derivatives such as **125**), the (1*Z*)-configuration is trapped in the products independently of the nature of the electrophile (Schemes 13 and 14). Accordingly, the carbamoyloxy group prefers the *endo* position in the reacting species **88**.

d) The 2,3-bond in the lithiated (*E*)- and (*Z*)-2-butenyl derivatives **101** and **102** is torsionally stable at $-70\,^{\circ}C$[98,101,102] since metalation and silylation take place "stereodefensively"[103] (Scheme 14).

e) The carbonyl addition shows a high preference for the γ-position. This is further enhanced by increasing γ-substitution in the allylic moiety.

f) The regiochemistry of alkylation and silylation (Scheme 14) is largely controlled by the position of the alkyl groups present. The carbamoyloxy group has very little influence[72b,104].

Thus, the species **88** exhibit properties typical of both allyl anions[102,105] and covalent allylmetal compounds[88]. Accordingly, they are probably best described as tight ion



Scheme 14. Regio- and *cis/trans*-selectivity of silylation [72b] and alkylation [104] of some lithium compounds **88**. In the *cis/trans* mixture of isomers the amount of **127**, **129**, **130**, **131**, **133**, **135** and **137**–**139** is more than 97% in each case.

pairs (Fig. 1, formulated for **94b**) in which the carbamoyloxy group positions the lithium ion at the α-carbon atom above the π surface[106]. Two further coordination sites of the cation are occupied by the diamine TMEDA.

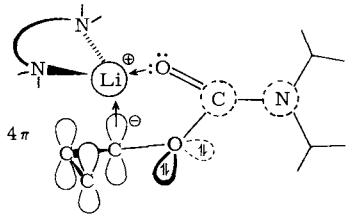
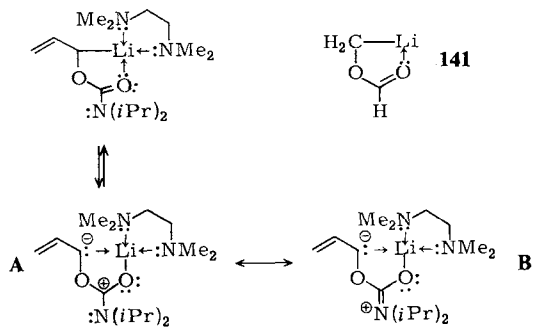


Fig. 1. Assumed structure of the carbamoyloxyallyllithium compound **94b**·TMEDA (type **88**) [96], cf. Scheme 15.

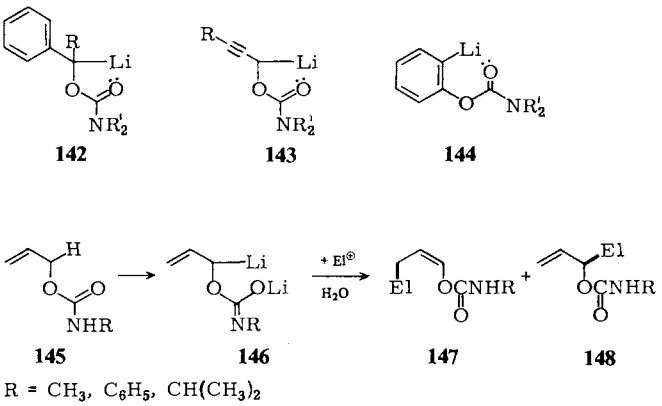
The favorable chelation should contribute to the stabilization of **88** in addition to its entropic share since the interaction between the cation and the oxo group increases the acceptor properties of the carbamoyloxy group according to the resonance formulas **A** and **B** (Scheme 15, "induced dipole stabilization")[107,108]. The importance of this factor is underlined by ab initio SCF calculations on lithiomethyl formate **141** by *Houk, Beak,* and *Schleyer*[109].



Scheme 15. Induced dipole stabilization of **94b**·TMEDA (cf. Fig. 1).

The complexing power of the carbamoyloxy group is also the reason for the high kinetic acidity of carbamic acid esters **87**. Results obtained by *Beak* et al.[110] and *A. I. Meyers* et al.[111] for similar cases indicate the existence of a pre-equilibrium with a complex composed of the substrate **87**, *n*-butyllithium, and TMEDA. This sets the course for a rapid deprotonation.

The activating and stabilizing influence of *N,N*-dialkylcarbamoyloxy groups also provides its worth in the generation of corresponding α-oxybenzyl-[93,112] and 1-oxyalkynyllithium[113] compounds of the types **142** and **143**, as well as in the *ortho*-lithiation of aryl carbamates to **144** as more recently shown by *Snieckus* et al.[114] (Scheme 16).



Scheme 16. Various lithiated carbamic acid esters.

Allyl *N*-phenyl- or *N*-alkyl carbamates **145**, prepared from allyl alcohol and isocyanates, are doubly deprotonated by *n*-butyllithium[115], giving the dilithio derivatives **146**. The carbonyl group in the latter is sufficiently protected "electronically" toward nucleophilic attack because of resonance; "small" *N*-substituents here are sufficient. Subsequent alkylation, silylation, or sulfenylation gives (*Z*)-enolic carbamates **147** with 65–97% *rs* besides the α-adducts **148**. Regrettably, satisfactory results have so far only been obtained with the parent compound[104]. According to *Gompper* and *Wagner*[81], the improved γ-selectivity in alkylation and silylation exhibited by **146** compared to **94b** (Scheme 11) is explained by a stronger donating power of the oxy group; this, however, also decreases the stability of the allyl anion.

7. Diastereoselective Homoaldol Additions

7.1. Metal Exchange—The Key to Higher Regio- and Diastereoselectivity

Allylmetal compounds with covalent metal-carbon bonds show appreciable chemo-, regio-, and diastereoselectivity in the addition reaction with aldehydes[88]. In cases where the configurations of starting materials and products have been unambiguously correlated[88a], the stereochemical results are best interpreted on the basis of the Zimmerman-Traxler model[116,117]. This assumes that the addition proceeds through six-membered chair-like transition states whose energies are qualitatively described by

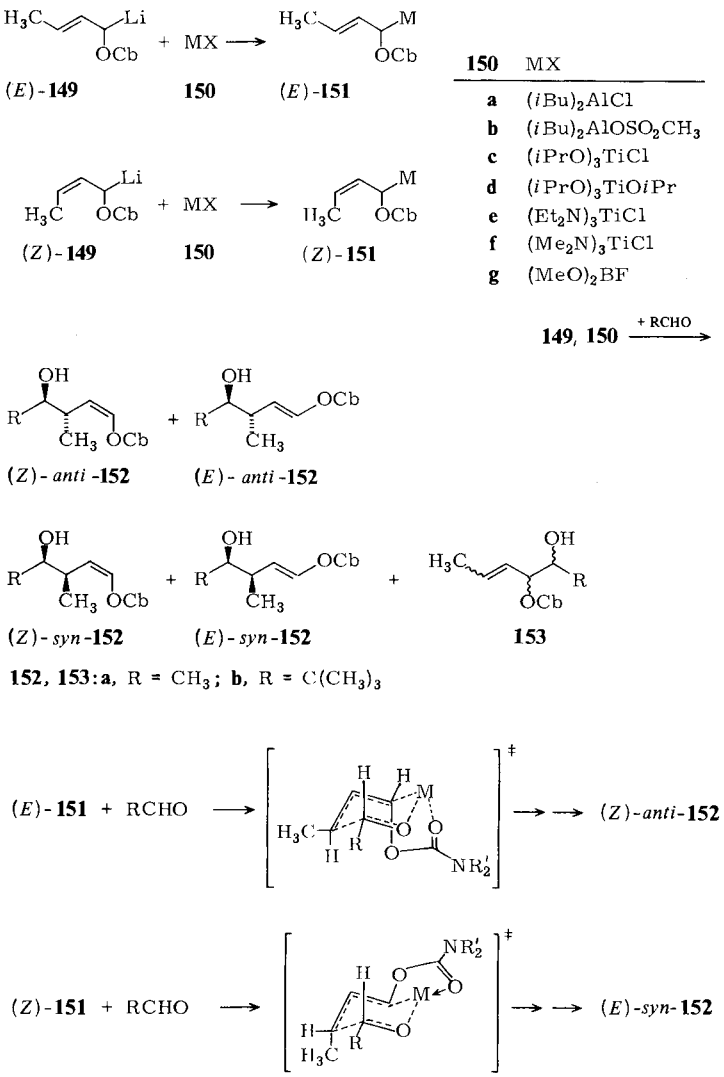
the same rules as for substituted cyclohexanes. In other words, whereas the position of the C-3 substituent is determined by the configuration of the allyl residue[118], the aldehydic alkyl group seeks to attain a (pseudo)equatorial position. Thus, (2*E*)-carbamates **151** should give predominately *anti*-adducts[4] **152** in a *lk*-process[5], as is also true for other allylmetals[88]. In contrast, (2*Z*)-carbamates should furnish the *syn*-diastereomers **152** in a *ul*-process. In both cases, the products will be in racemic form[119] (Scheme 17). As it turned out, the energy differences between the competing diastereomeric transition states are insufficient for the lithium compounds (*E*)- and (*Z*)-**149**[72b,96] (Table 1). This obviously suggested improving them by metal exchange.

Which cation is the most appropriate? Exchanged for lithium it must reliably occupy the 1-position, independently of the substituent pattern, i.e., it must respond well to complexation with the carbamoyloxy group. Furthermore, the metal should carry large, rigidly oriented ligands so as to ensure a high degree of diastereoselectivity[1]. In order to ascertain uniform prochirality of the starting materials, the metal exchange must not alter the geometry of the 2,3-bonding in **149** (stereodefensive strategy[103]), or, if it does cause equilibration, this should be rapid and lead completely in one direction (stereoconvergent strategy[103]).

The choice fell to di(isobutyl)aluminum derivatives (since work by *Still*[120] had indicated configurational stability of (*Z*)-2-butenylaluminum) and especially to titanium(IV) reagents, which had come into focus through work by *Reetz*[121] and *Seebach*[122]. Solution of the lithium compounds (*E*)- and (*Z*)-**149** were treated below −70°C with at least equimolar amounts of the metal reagents **150**; the allylmetal compounds **151** reacted at this temperature[123] with acetaldehyde or 2,2-dimethylpropanal to give the adducts **152a**, **b** and **153a**, **b**[124,125,100,101]. The regio- and diastereomeric ratios were in most cases determined by capillary column gas chromatography (Table 1).

The *anti/syn*-selectivities obtained for the lithium derivatives (*E*)- and (*Z*)-**149** are of a similar order of magnitude as observed by *Hayashi* et al.[71a] for butenyl dithiocarbamates **76** and by ourselves[72a,b] for the corresponding *S*-butenyl thiocarbamates **77**; yet the change from *S*- to *O*-esters causes a pronounced shift in favor of the (*Z*)-isomers.

With titanated (*E*)-2-alkenyl carbamates virtually only the (*Z*)-*anti*-adducts are obtained[125,126] (cf. also Scheme 18). In most cases very good (*Z*)-*anti*-selectivities are ob-



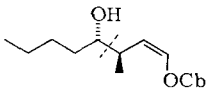
Scheme 17. Stereochemistry of the addition of metalated (*E*)- and (*Z*)-2-butenyl carbamates to aldehydes [119].

Table 1. Yields and diastereo- and regioselectivities of addition of metalated butenylcarbamates **149** and **151** (= **149** + MX) to acetaldehyde and 2,2-dimethylpropanol.

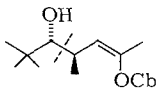
Allyl compound	MX **150**	R in RCH=O	Yield [%] [a]	**152** : **153** γ : α	**152**, Rel. Yield [%] *Z-anti*	*E-anti*	*Z-syn*	*E-syn*
(*E*)-**149**		Me	76	80 : 20	55	0	45	0
(*E*)-**149**	(*i*Bu)$_2$AlCl **150a**	Me	88	91 : 9	13	78	<1	8
(*E*)-**149**	(Et$_2$N)$_3$TiCl **150e**	Me	92	99 : <1	97	0	3	0
(*E*)-**149**		*t*Bu	80	84 : 16	85	0	15	0
(*E*)-**149**	(Et$_2$N)$_3$TiCl **150e**	*t*Bu	96	99 : <1	99.8	0	0.2	0
(*E*)-**149**	(MeO)$_2$BF **150g**	*t*Bu	89	77 : 23	41	18	4	37
(*Z*)-**149**		Me	73	83 : 17	12	12	18	58
(*Z*)-**149**	(*i*Bu)$_2$AlOMs **150b**	Me	88	99 : <1	2	8	3	87
(*Z*)-**149**		*t*Bu	78	85 : 15	11	18	12	59
(*Z*)-**149**	(Me$_2$N)$_3$TiCl **150f**	*t*Bu	92	99 : <1	60	20	9	11
(*Z*)-**149**	(MeO)$_2$BF **150g**	*t*Bu	87	75 : 25	28	12	8	52

[a] Yield of **152** + **153**.

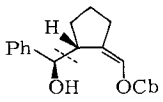
tained even after metal exchange with the easily accessible[121,122] tri(isopropoxy)titanium chloride **150c** or tetra(isopropoxy)titanium[127] **150d**. The more strongly "oxophilic"[121] tris(dialkylamino)titanium derivatives[128] **150e, f** give superior regioselectivities when the metallic moiety is "contrastedly" forced into the more highly substituted position or when ketones are used as reaction partners (see **159**, **158**, Scheme 18). Even prochiral ketones, e.g. acetophenone[129], are added in highly diastereoselective fashion[126]. So far the titanium variants have failed with 3-*endo*-substituted and (1*E*)-configurated lithium compounds[97,100] such as (*Z*)-**149**; the reasons for this are unclear[130].



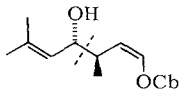
154 [a] 97%
rs,ds > 98% [126]



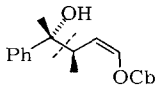
155 [b] 94%
rs,ds > 98% [97]



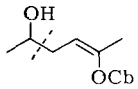
156 [a,b] 88%
rs > 97%, *ds* 96% [97]



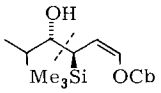
157 [c] 96%
rs > 97%, *ds* 97% [125]



158 [a, b] 75%
rs 85%, *ds* > 97% [126]
[d] 92%, *rs,ds* > 97% [99]



159 [d] 92%
rs > 97% [99]

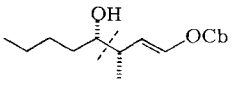


160 [d] 85%
rs,ds > 99% [98]

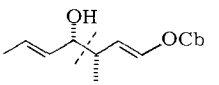
Scheme 18. Selectivities [119] and yields after metal exchange with titanium reagents. [a] With $ClTi(OiPr)_3$ **150c**. [b] With $Ti(OiPr)_4$ **150d**. [c] With $ClTi(NEt_2)_3$ **150e**. [d] With $ClTi(NMe_2)_3$ **150f**. Here, the diastereoselectivity (*ds*) is the amount of the relevant diastereomer in %.

(*E*)-*anti*-Adducts **152** predominate as products of the aldehyde addition of (*E*)-**149** after cation exchange with diisobutylaluminum chloride or methanesulfonate (**150a** or **b**)[124]. (*E*)-*syn*-Adducts **152** are obtained when aluminum derivatives of (*Z*)-configuration[101] (prepared from (*Z*)-**149**) are employed. However, the regio- and diastereoselectivities are smaller in both cases (Table 1; Scheme 19). The mesylate **150b**, freshly prepared from the hydride and methanesulfonic acid, turns out to be superior to the commercially available chloride **150a** in this respect[101,131]. The methyl pyruvate adduct **164** demonstrates that aluminum reagents discriminate quite well between ester and keto-groups. Apparently, however, dialkylaluminum groups respond more sensitively to the steric situation than to complexing with the carbamoyloxy residue; hence the γ-selectivity of the aluminum variants may be lost in unfavorable cases (cf. **166**)[97,99].

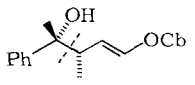
Exploratory experiments have shown that various boron reagents are unsuitable (e.g. **150g**)[132] because of poor reactivity, regioselectivity, and diastereoselectivity[100].



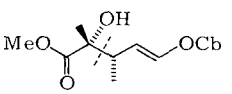
161 [a,b], 84%, *rs* 89%
ds 79 (85)% [101]



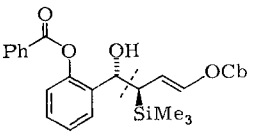
162 [a,c], 88%, *rs* 99%
ds 68 (86)% [101]



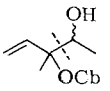
163 [a,c], 71%, *rs* 92%
ds 72 (82%) [101]



164 [a,c], 67%, *rs* 92%
ds 81 (87%) [101]



165 [c,d], 75%
rs,ds > 95% [98]



166 [b,e], 81%,
rs 90% [99]

Scheme 19. Selectivities [119] and yields after aluminum exchange. [a] Educt: (*Z*)-**149**. [b] Exchange with the chloride **150a**. [c] Exchange with the mesylate **150b**. [d] Educt: **104**. [e] Educt: **99**. In brackets: total *anti*- or *syn*-diastereoselectivity including the (*Z*)-derivatives.

7.2. Further *anti*-Diastereoselective Homoaldol Reactions

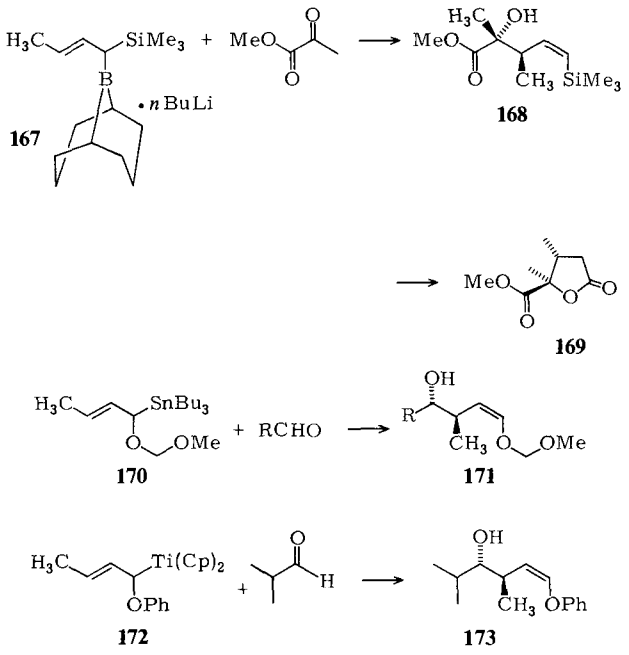
During the course of our work some further methods for the *anti*-diastereoselective homoaldol reaction with 1-heterosubstituted (*E*)-crotylmetal compounds became known (Scheme 20):

Y. Yamamoto et al.[133] added the borane **167** (as "ate" complex with *n*-butyllithium) to methyl pyruvate, giving the (*Z*)-*anti*-silane **168**, which in three further steps was transformed into methyl (±)-*cis*-crobarbate **169** in 70% yield. The low γ-selectivity (63% *rs*) together with the cumbersome preparation[134] of **167** currently make the method less attractive.

Thomas and *Pratt*[135a] used the stannane **170**, obtained from crotonaldehyde, tributylstannyllithium, and chloromethyl methyl ether, as a butanal-d^3-reagent. It reacts highly *anti*-selectively with aldehydes on warming to 140°C, giving the (*Z*)-enol ethers **171**. However, the yields were at most 40% (based on **170**).

Sato et al.[136] found that the bis(cyclopentadienyl)titanium(III) complex **172**, generated from the lithiated (*E*)-butenyl phenyl ether, gave the enol ether **173** with excellent (*Z*)-*anti*-selectivity on reaction with 2-methylpropanal. The scope of this procedure, however, is likely to be severely limited because of difficult access to higher metalated 2-alkenyl ethers[172].

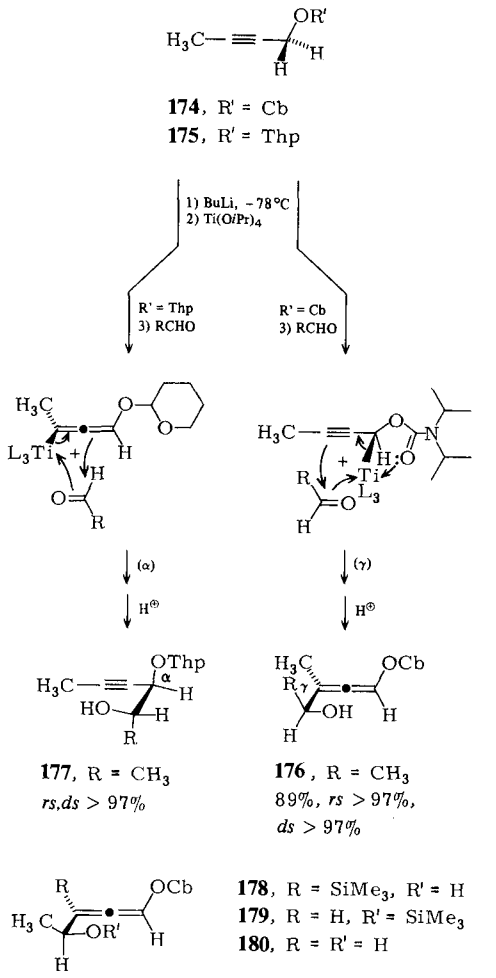
So far, no further methods for the *syn*-selective homoaldol reaction (see Section 7.1) have been reported[172].



Scheme 20. *anti*-Selective homoaldol reactions [119]. Cp = cyclopentadienyl.

7.3. Diastereoselective Allene Synthesis with Titanated Alkynyl Carbamates

The 2-butynyl carbamate **174** is rapidly deprotonated to the lithium compound under standard conditions. After exchanging the cation with titanium reagents such as **150c** or **d**, addition to aliphatic aldehydes gives diastereomerically pure α-allene alcohol **176** with over 95% *ds*[113]. The (*R*S**)-configuration[137] of the acetaldehyde adduct **176** has been established by an X-ray structure analysis of the phenyl urethane[138]. By lithium hydride induced rearrangement[139,140] of the 3-trimethylsilyl-derivative **178** to the ether **179** and subsequent fluoride-catalyzed desilylation, the allenes **180** with only one substituent on C-3 can also be obtained (90% *ds*)[141] (Scheme 21).



Scheme 21. Aldehyde addition of titanated 2-butynyl derivatives [119]. Cb = *N,N*-diisopropylcarbamoyl; Thp = 2-tetrahydropyranyl.

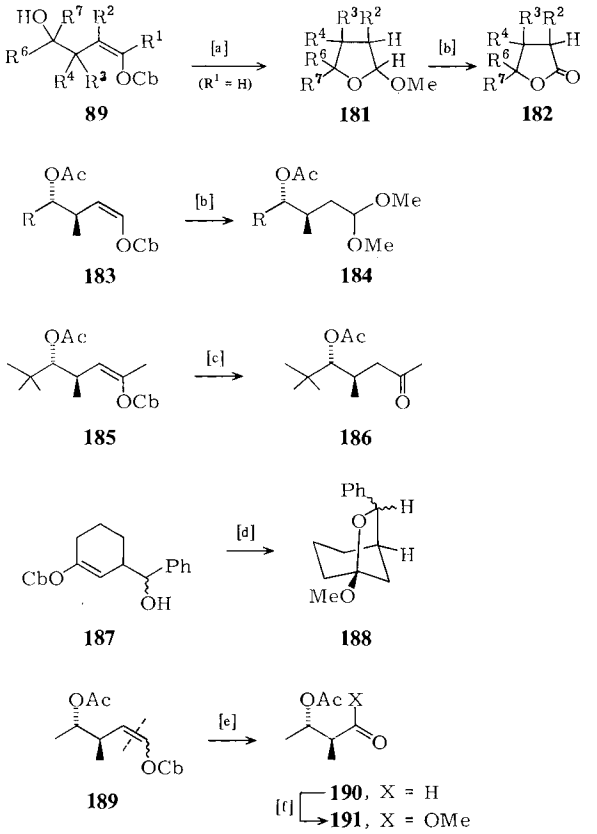
The reaction sequence is remarkable in two respects: According to a study by *H. Yamamoto*[142], the tetrahydropyranol ether **175** gives only the α-adduct **177** upon lithiation and titanation under conditions nearly identical with the above; an allenic titanium intermediate was indicated by IR spectroscopy. The complete inversion of regioselectivity upon changing the oxygen substituent clearly demonstrates the active role of the carbamoyloxy residue in locating the cation. A second surprise is the high degree of "simple diastereoselectivity" encountered on fusion of axial prochiral and centro-prochiral groups; such diastereoselective allene syntheses appear to have been unknown hitherto[144].

8. Transformations of the Enol Carbamates; Synthetic Applications

The enol carbamate moiety in the adducts of type **89** is unusually stable toward acid catalyzed solvolysis[144]: It survives heating with 2 N sulfuric acid in methanol or tetrahydrofuran/water for 2 h unchanged; at most, elimination or ether formation takes place at the 4-hydroxy group. Presumably, the donating power of the oxygen atom is strongly reduced due the presence of the electron-attracting dialkylcarbamoyl group, thus preventing stabilization of an intermediary α-oxy cation by the carbamoyloxy substituent. In addition it acts more basic than the olefinic double bond, as a "proton trap". The alternative, namely to initiate deblocking via an attack on the carbonyl group, is also deemed to fail because the sterically protected *N,N*-diisopropyl derivatives **89** are inert to sodium methoxide (methanol, 65 °C), lithium diethylamide (THF, 65 °C), lithium aluminum hydride (THF, 65 °C), and diisobutylaluminum hydride (dichloromethane, 20 °C)[97]. An attack on the double bond can be expected only from "softer" electrophiles, e.g. bromine, chlorine, peracids, mercury(II) or palladium(II) salts. The advantage of a decreased reactivity lies in maintaining the original carbonyl protection for several synthetic steps, thus often obviating the need to change it.

Deblocking is selective and effective under mild conditions: In the presence of 1 mol-% mercury(II) acetate or 0.5 mol-% of palladium(II) chloride as catalyst, together with methanesulfonic acid (to remove the liberated diisopropylamine) in the molar ratio 1:1, the methanolysis[124,126] of

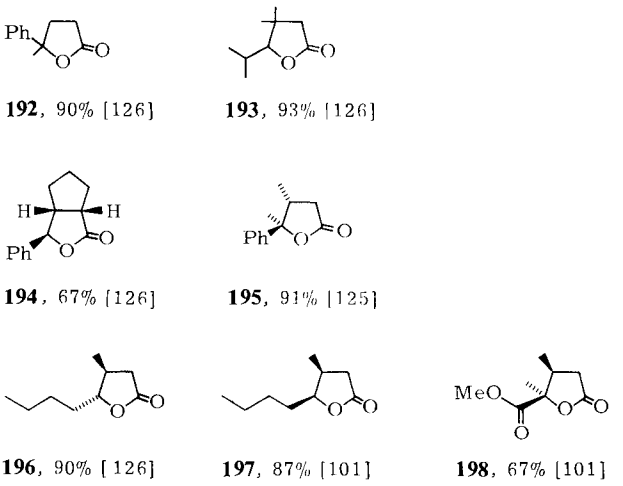
the adducts **89** ($R^1 = H$) proceeds rapidly at room temperature, giving *O*-methyl-γ-lactols **181** (Scheme 22). The corresponding dimethyl acetals **184** are obtained under the same conditions from *O*-protected derivatives such as the acetates **183**[124]. Direct hydrolysis of the adducts **89** to homoaldols **91** is possible if methanol is replaced by tetrahydrofuran/water[145]; however, the purification is made tedious because of the tautomeric equilibrium with γ-lactols **92**. Ketone-derived enolic carbamates such as **185** or **187** can, on the other hand, also be cleaved with titanium tetrachloride/methanol/water[72b] or boron tribromide/methanol[97]. Thus, (*Z*)-*anti*-**185** gives the diastereomerically pure ketone **186** in 90% yield on reaction with $TiCl_4$[72b],



Scheme 22. Deblocking of 4-hydroxyenol carbamates [119]. [a] Methanol, methanesulfonic acid, 1 mol-% mercury(II) acetate, 3—15 h, 20—30°C. [b] *m*-Chloroperbenzoic acid/boron trifluoride etherate, dichloromethane, 3—15 h, 20—30°C. [c] Titanium tetrachloride in dichloromethane, −78 to 0°C; methanol; water. [d] Ozone, dichloromethane/methanol, *p*-toluenesulfonic acid, −70 to −50°C; dimethyl sulfide. [e] Formic acid/hydrogen peroxide; diazomethane.

while the mixture of diastereomers **187** gives the bicyclic ketal **188** on treatment with BBr_3[97].

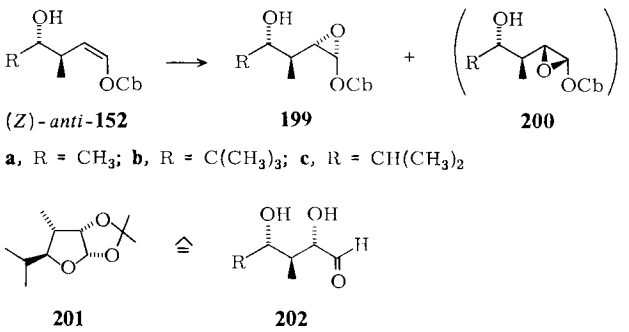
Oxidation[146] of 2-methoxytetrahydrofurans **181** according to the method of *Grieco* et al. furnishes the γ-lactones **182** in high yields[126, 101]. Examples are **192**—**195** and (±)-quercus lactone A **196**[126] and B **197**[101], components of oak bark, and (±)-*trans*-crobarbatic acid methyl ester **198**[101, 133], a degradation product of pyrrolizidine alkaloids (Scheme 23).



Scheme 23. γ-Lactones prepared from adducts of the type **89** [119, 101, 126].

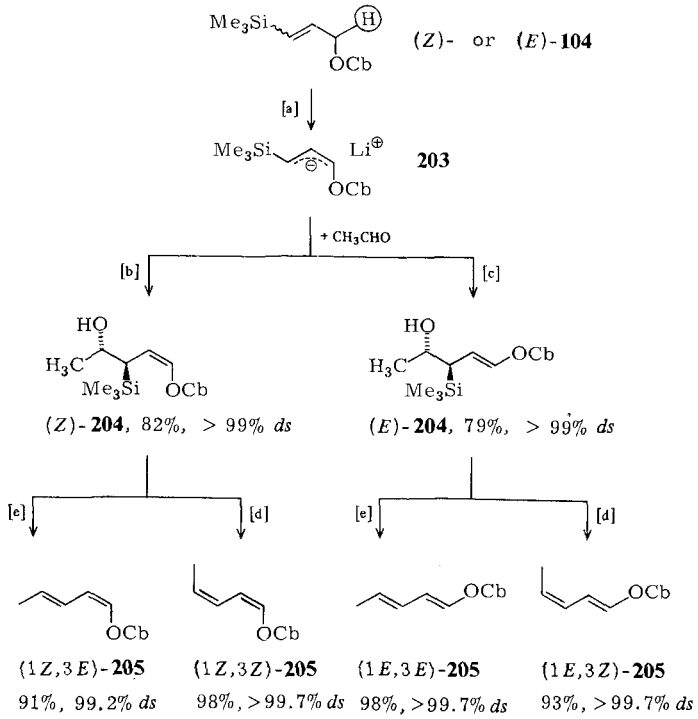
Ozonolysis of *O*-acetylated enolic carbamates such as **189** and subsequent reductive work-up affords the aldol acetates **190**; after oxidation[147] and esterification, the β-acetoxycarboxylic esters **191** are obtained (Scheme 22). In this way we correlated the relative configurations of the adducts **152** with those of stereochemically secured compounds[124].

The uniform prochirality of the enol double bond in the adducts **152** invites further stereocontrolled substitution. In analogy to the corresponding homoallyl alcohols (alkyl in place of OCb in **152**)[148], the epoxidation[149] of the adducts (*Z*)-*anti*-**152** proceeds highly diastereoselectively. Whereas *m*-chloroperbenzoic acid in dichloromethane at 0°C gives the diastereomers **199** and **200** in a ratio of 6 : 1, the vanadium-catalyzed oxidation with *tert*-butyl hydroperoxide[150] gives only the isomer **199** (>97%)[151, 152] (Scheme 24), whereby the selectivity is independent of the residue R. The relative configuration of the isopropyl-derivative **199c** was confirmed by X-ray structure analysis[153]. Although the epoxy carbamates **199** can be purified by chromatography or recrystallization without decomposition, they prove highly reactive under Lewis acid catalysis. Thus, reaction of **199c** with acetone/boron trifluoride furnishes the furanoid product **201** in 80% yield[151]. Accordingly, the oxiranes **199** correspond to diastereomerically pure (racemic) 2,4-dihydroxyalkanals **202**.



Scheme 24. Epoxidation of (*Z*)-*anti*-derivatives **152** [119, 151].

1-Oxy-1,3-alkadienes are attracting considerable interest as Diels-Alder components[154,155]. Each of the four possible 1,3-alkadienyl carbamates **205** can be obtained highly stereoselectively via the β-silyl alcohols **204**[98] (Scheme 25). The procedure is stereoconvergent in the first step[103] since only the (2*E*)-anion **203** is obtained after lithiation, irrespective of whether (*E*)- or (*Z*)-alkenyl carbamate **104** is used as the precursor[156]. The next two steps are now performed in a doubly stereodivergent manner: The titanium-mediated aldehyde addition gives the adducts (*Z*)-*anti*-**204** (>99% *ds*); the aluminum variant gives the isomeric (*E*)-*anti*-**204** (>99% *ds*). A subsequent Peterson elimination[157,158] determines the configuration of the newly created γ,δ-double bond in the alkadiene **205**. In basic media the stereospecific *syn*-silanolate elimination leads to the (*Z*)-configuration and hence to (1*Z*,3*Z*)- or (1*E*,3*Z*)-**205**. In contrast, Lewis acid catalyzed *anti*-elimination leads to a (3*E*)-double bond in (1*Z*,3*E*)- or (1*E*,3*E*)-**205**. Overall yields of 80% and purities of >99% (determined by capillary gas chromatography) are obtained in these reactions.



Scheme 25. Highly stereoselective synthesis [98] of 1,3-alkadienyl carbamates **205** [119]. [a] *n*-BuLi/TMEDA in ether/hexane, −78°C, 1 h. [b] $ClTi(NMe_2)_3$ **150f**; aldehyde, 3 h at −78°C to −70°C; chromatography or crystallization. [c] $CH_3SO_2OAl(iBu)_2$ **150b**, otherwise as in [b]. [d] 2.5 mol equivalents of sodium hydride, THF/ether, 3 h at 0°C. [e] 2.5 mol equivalents of $BF_3 \cdot OEt_2$, 15 h at −78°C.

9. The Challenge: Asymmetric Homoaldol Reactions

We have so far considered only racemic homoaldols. In order to synthesize these in optically active form, only one of the reaction partners need, in principle, be enantiomerically pure. The art is to find the conditions whereby the auxiliary chirality center induces high asymmetry on the newly created one[159]. This means that ΔG^{+} of the competing diastereomeric transition states should differ by at least 1.5 kcal/mol (corresponding to ≥98% *ds* or ≥96% *ee* at −78°C). In principle, asymmetric induction can originate in the allylic moiety of the homoenolate reagent, in the dialkylamino group, in the counterion M or its ligand sphere, or in the carbonyl compound (Fig. 2).

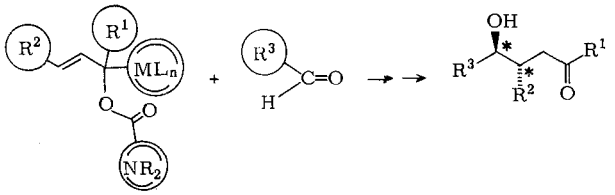
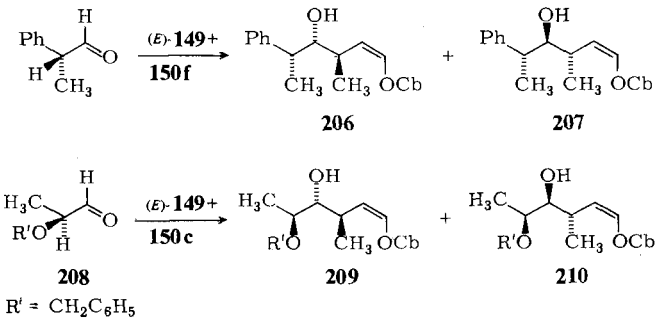


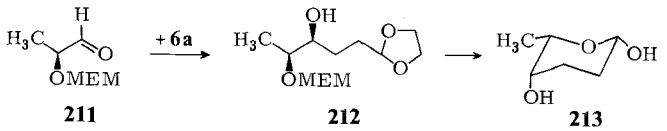
Fig. 2. Theoretically possible asymmetric homoaldol reactions. For explanation see text.

The lithium compound derived from the carbamate **108** of (−)-myrtenol gives a single adduct **122** with cyclopentanone[96] (Scheme 13). The good stereodifferentiation is a result of the diastereotopic faces of the rigid bicycle **108**. Promising results are also obtained with α-chiral aldehydes: Of the eight possible diastereomers only two, *rac*-**206** and *rac*-**207** (ratio 93:7) are obtained from racemic[160] 2-phenylpropanal with the titanium reagent (*E*)-**151f**[161] (Scheme 26). Here, one reaction step at once controls (93% *ds*) the relative configurations of three chirality centers and two prochirality centers. (*S*)-2-Benzyloxypropanal **208**, obtainable from ethyl lactate in two steps[162], reacts with lower diastereoselectivity under standard conditions, but not all possibilities for steric approach control or chelation control[163] have been exhausted. The two optically active (*Z*)-*anti*-diastereomers **209** ("Cram adduct") and **210** ("*anti*-Cram-adduct") are obtained in a 70:30 ratio using the titanium reagent (*E*)-**151c**[161]. The lower selectivity is compensated by the fact that the two isomers of very differing polarity are already separated by filtration through silica gel.



Scheme 26. Homoaldol reactions with α-chiral aldehydes.

The classical reagent **6a**[10] is a good choice when only the incorporation of an unsubstituted propanal-d^3-unit in a chiral 2-alkoxyalkanal is required: *Kelly* et al.[164] obtained **212** with 95% *ds* by chelation-controlled addition from the (*S*)-2-[(2-methoxyethoxy)methoxy]propanal **211** at −100°C. After removal of the protecting group the antibiotic sugar L-rhodinose **213** was obtained in an overall yield of 48% based on **211** (Scheme 27).

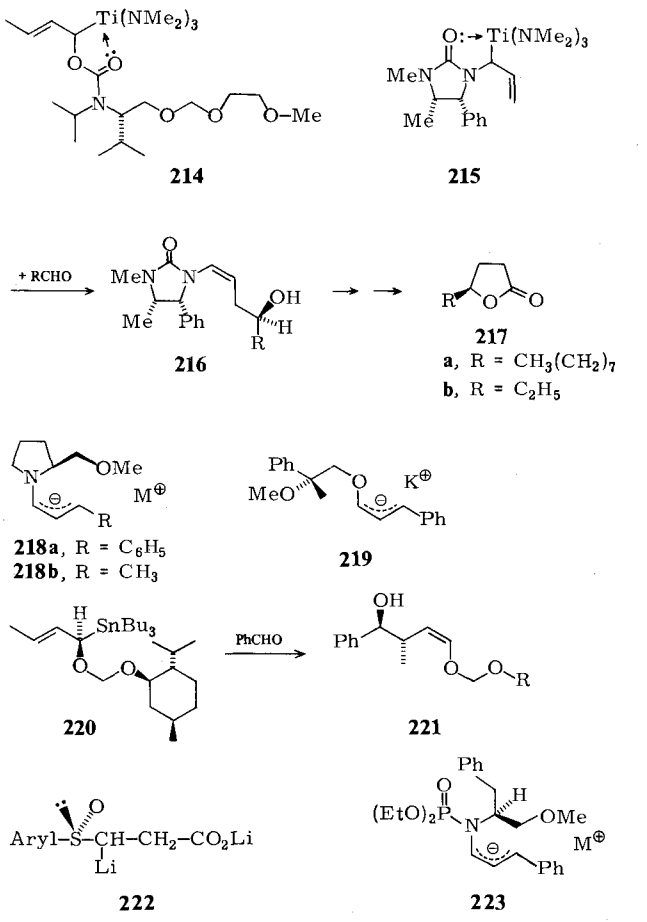


MEM = $CH_3OCH_2CH_2OCH_2$

Scheme 27.

A wider variety of target molecules are accessible using reactants with detachable auxiliary groups (doubly circled in Fig. 2). We therefore examined the butanal-d^3-reagent **214**, whose amide group originates in (*S*)-valinol[165] (Scheme 28). Although high (*Z*)-*anti*-selectivity is maintained in the addition to acetaldehyde, the diastereomeric ratio is at best 60:40. The direction of the induction was not determined.

Better results were obtained by *Helmchen* et al.[166] using a rigid system, fixed through a favorable intramolecular complexation. The allylurea derivative **215** obtained in a short sequence from (−)-ephedrine adds with high diastereofacial selection (94—98% *ds*) to aliphatic aldehydes and to some prochiral ketones. The minor isomer *epi*-**216** is almost completely removed by recrystallization. Methanolysis of **216** and subsequent Grieco oxidation[146] affords the enantiomerically pure γ-lactone **217**; *ent*-**217a** and **b** occur in nature as insect pheromones. It is still questionable, however, whether the system can be extended to substituted and less acidic allylureas. Although the magnesium



Scheme 28. Asymmetric homoenolate reagents.

derivative (MgBr in place of $Ti(NMe_2)_3$ in **215**) exhibits high γ-regioselectivity just like its achiral prototype[51], it shows no stereoselectivity.

Two chiral 3-phenylpropenal-d^3-reagents have been used for asymmetric alkylation; **218a** by *Enders* and *Ahlbrecht* et al.[167,173] and **219** by *Mukaiyama* et al.[168]. In the alkylation, silylation and phosphorylation reactions, the butenyl derivative **218b** generally gives diastereomeric excesses of between 85 and 95% *de*, but the γ-regioselectivity rarely exceeds 70%[174]. Chiral phosphoramidates, such as **223** react with only moderate diastereoselectivity[173]. Homoaldol reactions with the reagents **218**, **219** and **223** have so far not been reported; the problem may lie in the control of regioselectivity.

A remarkable result has just been published by *E. J. Thomas* et al.[135b]: The stannane **220**, obtained by chromatographic separation of the diastereomers, adds to benzaldehyde giving the enol ether **221** with practically complete transfer of chirality (>98% *ee*). Equally efficiently, 1-*epi*-**220** induces the opposite configuration of the newly created chirality center. The chiral dilithiated sulfoxide **222** has recently been used by *Bravo* et al.[21] in the synthesis of enantiomerically pure butenolides of the type **24**. However, moderate asymmetric induction necessitates separation of the diastereomers.

10. Outlook

In the five years that have passed since the first reported studies in this sector, homoaldol reactions with metalated *N,N*-diisopropyl carbamates have reached a high standard, comparable to the racemic variants of the aldol addition as regards scope, regioselectivity and diastereoselectivity. Properly scheduled in a synthetic scheme, there is a good chance that homoaldol reactions will do their job well. However, the "homoaldol retron" is rarely openly incorporated in the natural products whose synthesis is challenging, for the homoaldol reaction is "antibiomimetic". Nature does not appear to use it. At the same time, this is an advantage, which will incite the development of new synthetic strategies. Thus, an exceedingly flexible route to branched desoxy sugars with various chain lengths, substitution patterns, and relative as well as absolute configurations, can already be envisaged. In this process, optically active hydroxyaldehydes are extended by three C-units. The option of stereocontrolled 1,2-epoxidation of enol carbamates further extends the access to polychiral structures.

The "chiralization" of our homoenolate reagents is a stimulating problem for a method-oriented research group. We see the most promising possibility of asymmetric homoaldol reaction in the incorporation of an asymmetric "cation" M, because this will be in close contact with the developing chirality center at C-4. The promising results obtained by *R. W. Hoffmann*[88a], *Midland*[169], *Matteson*[170], and *H. C. Brown*[171] with allyl boranes, and by *Reetz*[121] and *Seebach*[122] with chirally modified titanium reagents, as well as our own experience from unsuccessful attempts at this chiralization[165], make the solution appear tangibly close.

Our own work has enjoyed continuous and generous support by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie. Thanks are due to my co-workers, whose names will be found in the references, and in particular to Dr. Rudolf Hanko, who during his graduate work, untaunted by initial failure, brought an idea that had been conceived on paper to a successful conclusion. The determinations of configurations were greatly facilitated by X-ray analyses; we thank Professor G. M. Sheldrick, Dr. E. Egert and Dr. P. G. Jones, Institut für Anorganische Chemie der Universität Göttingen, for extremely valuable cooperation.

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The Dendralenes— a Neglected Group of Highly Unsaturated Hydrocarbons

By Henning Hopf*

Dedicated to Professor Wolfgang Lüttke on the occasion of his 65th birthday

Dendralenes are acyclic and cyclic cross-conjugated polyolefins derived from 3-methylene-1,4-pentadiene. This review summarizes and compares, for the first time, the methods developed for the synthesis of this class of hydrocarbons. Because of their particular arrangement of π-electrons, the dendralenes are novel substrates for addition and rearrangement reactions, and model compounds for spectroscopic studies.

For where will it get one, on the Day of Judgment, when mankind's works are weighed in the balance, to come forward with three treatises on formic acid—or thirty, for that matter? On the other hand, what can one know about the Day of Judgment if one does not even know what may have come of formic acid by then?

Robert Musil[1].

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).

Roald Hoffmann[2].

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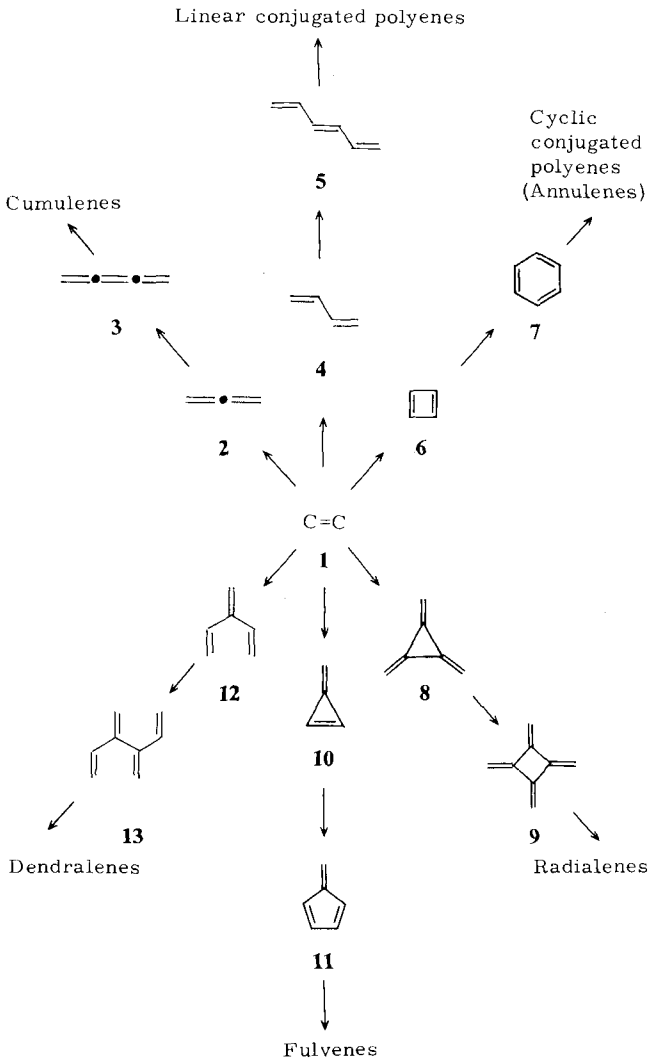
1. Polyenes by Coupling Ethylene Units

After considerably more than a hundred years of scientific work on hydrocarbons, one might assume that everything "that may come of" the two basic elements of organic chemistry is known. This may be the case "on paper"; in reality, however, in the preparation or the study of the chemical properties of many hydrocarbons, this is far from true. Even today many groups of compounds in this class of substances are represented by a few examples only, many of which have often only been studied cursorily. There are often no comparative studies of reactivity, as illustrated here using the example of the polyolefins.

Neglecting molecules with isolated double bonds, we can use the fragment "C=C" **1** to construct the basic types summarized in Scheme 1.



Scheme 1. Construction of polyolefins from ethylene building blocks (schematic).

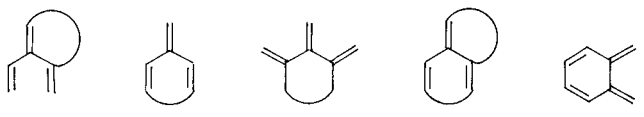
Coupling etheno units via common carbon atoms leads to allenes **2**[3,4] and cumulenes **3**[4]. If the C_2-units are connected via single bonds, conjugated di- **4**, tri- **5**, and finally polyenes are formed. Contrasting with this linear coupling is a cyclic one, which produces—via cyclobutadiene **6** and benzene **7**—the cyclic, conjugated polyenes, the annulenes. In this group of hydrocarbons the double bond always occupies an endocyclic position. The so-called radialenes, on the other hand, have entirely exocyclic double bonds, the simplest representatives being [3]radialene **8**[5] and [4]radialene **9**[6]. If both types of double bond arrangements occur in the polyolefin, fulvenes result, triafulvene **10**[7] and fulvene **11** being the simplest members.

Of the compounds presented so far, the conjugated acyclic and cyclic systems have been the most extensively investigated and occupy a central role in organic chemistry. However, compounds with cumulated double bonds are also beginning to enjoy a steadily increasing interest[3,4]. The number of the radialenes is still quite small. Among the parent systems, for example, the next higher homologue of **9**, [5]radialene, is still unknown. On the other hand, the radialenes form the parent molecules of the, in the meantime, quite thoroughly investigated oxocarbons and their derivatives[8]. The fulvenes and their derivatives exhibit a broad structural richness and varied chemical behavior, as shown recently by *Prinzbach* et al.[9], *Neuenschwander* et al.[10a,11], and *Hafner* et al.[10b]. Fulvenes and radialenes are so-called *cross-conjugated* systems and are their most important *cyclic* representatives. Far less is known, on the other hand, about *acyclic cross-conjugated* polyenes. These so-called *dendralenes*[12] are formally derived from the building block **1** by 1,1-coupling: the simplest dendralene is therefore 3-methylene-1,4-pentadiene **12**, and the next higher homologue is 3,4-bismethylene-1,5-hexadiene **13** ([4]dendralene). Dendralenes may also be formally derived by rupture of certain C–C bonds of cross-conjugated cyclopolyolefins: for example, **13** is obtained from **9** by cleavage (and saturation) of one cyclobutane bond, and **12** from **11** by removal of the C_3–C_4 bond. In fact, *Staudinger*, who was among the first to prepare a derivative of **12** (see Section 2.1), called these compounds "open fulvenes"[13].

In recent years cross-conjugated molecules of the dendralene type have received increasing attention. Rather than merely isolating and characterizing these hydrocarbons, more and more workers are attempting to synthesize specifically substituted and functionalized dendralenes. On the one hand, this growing interest has its roots in preparative chemistry. Dendralenes, for example, are suitable educts for multiple additions of the Diels-Alder type (see Section 2.1), since each addition of a dienophile molecule generates a new diene system which can undergo further cycloaddition. With the aid of dendralenes, therefore, large sections of the carbon framework of complex polycycles may, in principle, be built up. In thermal and photochemical rearrangements, novel results are to be expected, too, since the dendralenes should undergo these reactions like some of the other π-systems shown in Scheme 1.

On the other hand, molecules like **12** and **13** are also interesting from the structural viewpoint since a priori it is not at all clear whether they should prefer a planar structure. In fact this is not very likely, as discussed in Section 3. Unsaturated hydrocarbons have always been preferred as model compounds for spectroscopic studies, and the dendralenes are no exception in this respect[103–108]. Finally, cross-conjugation is a commonly encountered phenomenon in natural product and dyestuff chemistry, although in

the majority of cases the various π-systems are polarized either by heteroatoms and/or by electron-donating or -accepting substituents. This review article summarizes the preparative methods leading to this group of polyolefins; cyclic molecules are also included, if the ring-producing structural element does not generate radialenes, fulvenes, or related structures (see Section 3). Appropriate derivatives of **12** would for example be the bridged compounds **14**—**17**. This restriction also precludes the preparatively extraordinarily useful *o*-quinodimethanes **18**[14,15]—quasi "shortcircuited" [4]dendralenes—from this review.



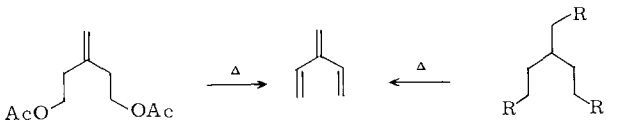
14 **15** **16** **17** **18**

As an ordering principle in this article, the degree of structural complexity of the target molecules, and not the various methods of preparation was selected. It comes as no surprise that among these, the standard methods for the preparation of double bonds occur widely (above all, eliminations and Wittig reactions). However, as a novel and variable synthetic approach to the dendralenes, thermal isomerization of polyenes, alkynes, and allenes has recently gained importance.

2. Acyclic Dendralenes

2.1. 3-Methylene-1,4-pentadiene 12 ([3]Dendralene) and its Derivatives

Although the first derivatives of **12** were prepared around the turn of the century (vide infra), the parent hydrocarbon was only synthesized in 1955. Ester pyrolysis of the readily available diacetate **19**[16] (485 °C, flow tube) as

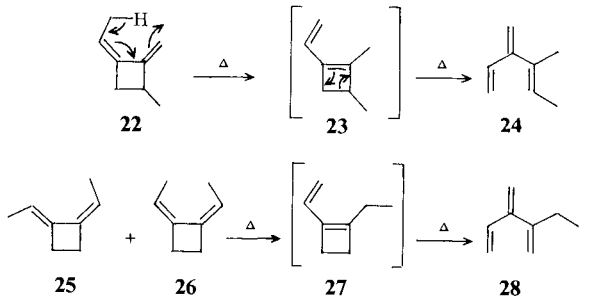


19 **12** **20**, R = OAc; **21**, R = $^{\oplus}NMe_3\ OH^{\ominus}$

well as of the triacetate **20**[17] (540 °C, flow tube) afford **12** in acceptable yields (ca. 30 and 45%, respectively). In a novel variant of this approach, the triene is obtained by Hofmann elimination of the ammonium salt **21**[18].

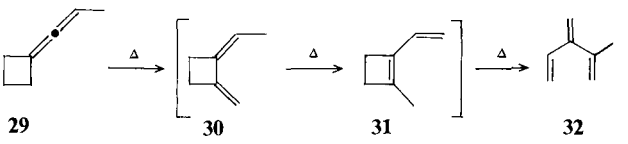
Several alkyl derivatives of **12** have been prepared by thermal isomerizations. Gas-phase pyrolysis of **22** at 260 °C leads to (4*E*)-3-methylene-4-methyl-1,4-hexadiene **24** in 90% yield, presumably by two successive concerted reactions (1,5-hydrogen shift to **23**, which undergoes electrocyclic ring opening[19]). **25** and **26** isomerize analogously via the presumed intermediate **27** to the 2-ethyl derivative **28**[19].

Preparatively even simpler is the thermal rearrangement of the propenylidenecyclobutane **29**, which is readily con-



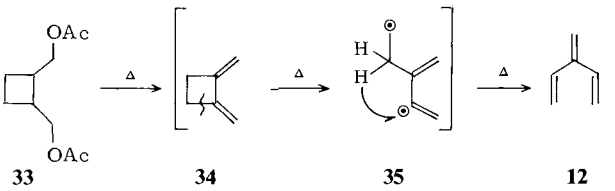
22 **23** **24** **25** **26** **27** **28**

verted into **32** by gas-phase pyrolysis[20]. The most probable intermediates in this reaction are the (not isolated) diene isomers **30** and **31** of **29**, the driving force of the process being provided both by the ring strain of **29** and



29 **30** **31** **32**

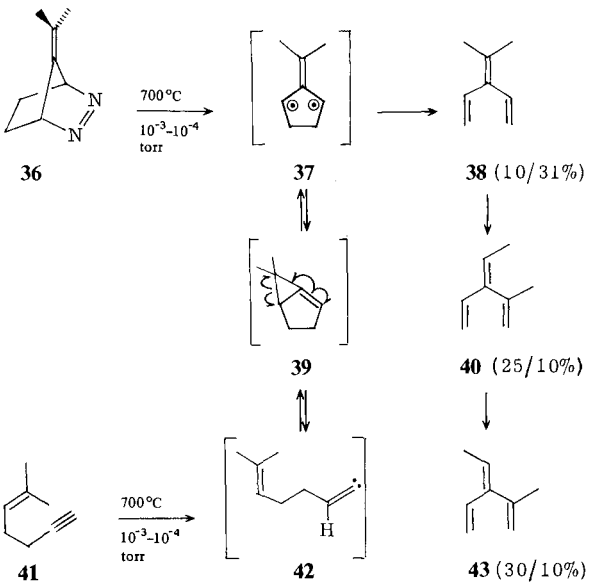
by the high energy of the allene group[21]. Hydrocarbon **12** is possibly also formed from 1,2-dimethylenecyclobutane **34**. In several attempts[22,23] to prepare **34** by ester pyroly-



33 **34** **35** **12**

sis of **33** the only hydrocarbon isolated was small amounts of [3]dendralene. Its formation can be rationalized by "vertical" cleavage of the four-membered ring of the initially produced **34**. The diradical **35** can subsequently stabilize itself by a 1,3-hydrogen shift.

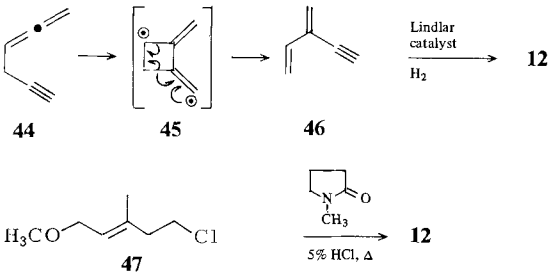
Using a completely different, but nevertheless pyrolytic route, *Berson* et al. prepared the methyl [3]dendralenes **38**,



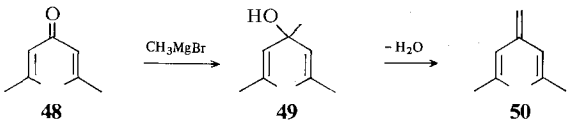
36 **37** **38** (10/31%) **39** **40** (25/10%) **41** **42** **43** (30/10%)

40, and **43**[24]. These trienes are formed, on the one hand, by vacuum flash pyrolysis of the diazene **36**, whereby **38** is the initially formed product, which subsequently equilibrates to **40** and **43** via 1,5-hydrogen shifts. The 2-isopropylidene-1,3-cyclopentanediyl **37** initially produced from **36** by N_2 loss is, on the other hand, also accessible via a remarkable series of rearrangements from the enyne **41**. By means of the well-known isomerization of terminal alkynes to vinylidenecarbenes, **41** rearranges to **42**, which ring-closes to afford the bicyclo[3.1.0]hex-1-ene **39**; finally **39** undergoes ring-opening to give **37**. The yields given in the second position of the parentheses for **38**, **40**, and **43** refer to the last-mentioned route.

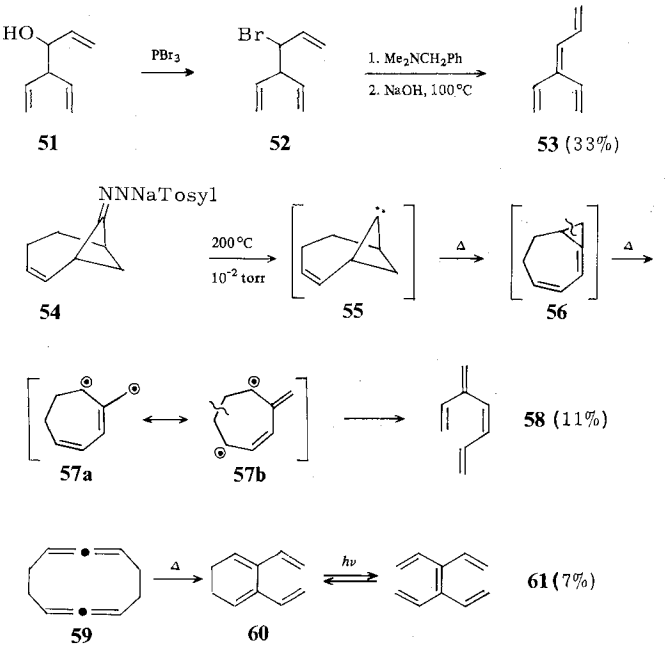
An acetylene derivative has also been employed in the preparation of the simplest cross-conjugated dienyne **46**[25]. Gas-phase pyrolysis of 1,2-hexadiene-5-yne **44** furnishes 3-methylene-1-penten-4-yne **46** in ca. 45% yield. The mechanism of this formal 1,3-ethynyl migration is unknown; however, the diradical **45** is a conceivable intermediate[26]. Lindlar hydrogenation of **46** affords another route to 2-vinyl-1,3-butadiene **12**[27], which can also be produced by subjecting 5-chloro-3-methyl-2-pentenyl methyl ether **47** to a multiple elimination sequence[28].



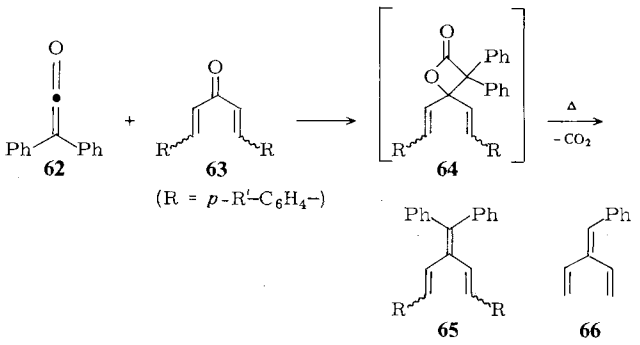
Cross-conjugated dienones have been employed occasionally for the preparation of the corresponding trienes (cf. Section 3.1). In a very early example, Grignard reaction of phorone **48** provided the tertiary alcohol **49**, which during distillation dehydrates to the tetramethyl[3]dendralene **50**[29].



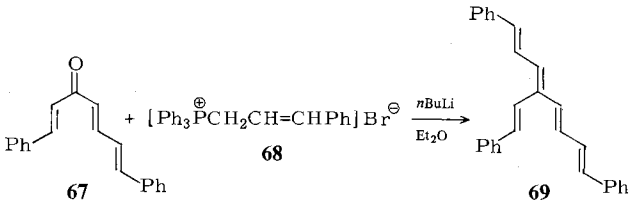
Several vinyl[3]dendralenes have been prepared by eliminations (**52**→**53**[30]) and rearrangements (**55**→**58**[31]; **60**→**61**[32]). Whereas multistep isomerization of the carbene **55**—prepared by vacuum flash pyrolysis of the sodium salt of bicyclo[4.1.1]oct-2-en-7-one tosylhydrazone **54**—is unspecific (in addition to 5-methylene-1,3,6-heptatriene **58**, at least six other hydrocarbons are formed[31])—photoisomerization of **60**, which itself is a (bridged) [4]dendralene (see Section 3.1) leads exclusively to **61**[32]. As precursor for **60** an allenic hydrocarbon **59** is used once again (cf. Section 3.3).



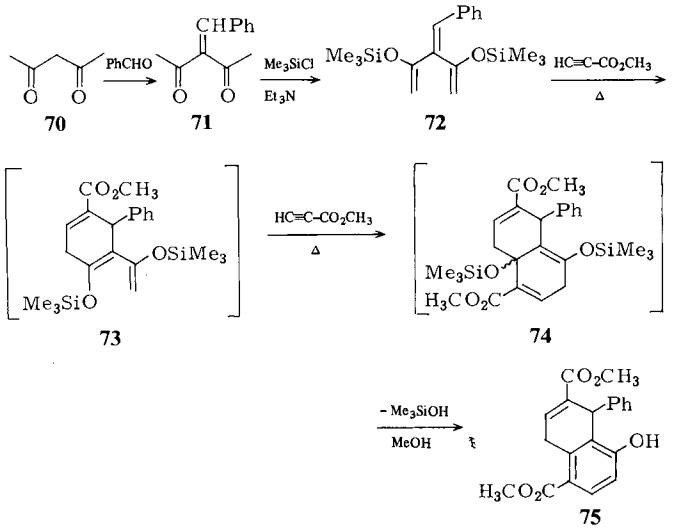
The phenyl derivatives **65**, *Staudinger*'s "open fulvenes", previously referred to, have been known for decades. They are produced by addition of diphenylketene **62** to *p*-substituted dibenzylidene acetones **63** (R′=H, CH_3O, Cl, styryl), with the (not isolated) β-lactone **64** as primary adduct. The reaction fails with the phorone **48**[33]; however, in view of the currently available, much more reactive ketenes[34] this elegant approach employing easily obtainable substrates should be reinvestigated. Dehydrobromination of 3-(bromo(phenyl)methyl)-1,4-pentadiene with potassium hydroxide in methanol provides the monophenyl derivative **66** of [3]dendralene[35].



The Wittig reaction has apparently not—or only unsuccessfully—been used to prepare alkyl derivatives of **12**. In marked contrast is the aryl-substituted series, where *Bohlmann* has described the synthesis of numerous cross-conjugated hydrocarbons. A case in point is provided by the olefination of **67** with the ylide from **68** to afford **69**.

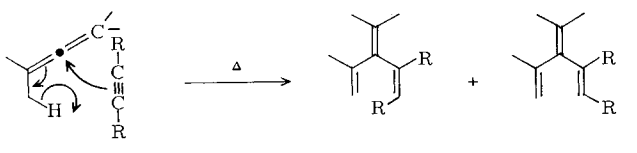


The dendralenes described so far in this section are useful model compounds for the investigation of the stereochemical and spectroscopic properties of the different connectivity and substitution types, and can also be used to study the elementary reaction modes. For the solution of more demanding synthetic tasks, the value of the unsubstituted or alkyl, alkenyl, or aryl substituted hydrocarbons is limited. For these purposes more reactive and chemically more variable substituents are required. Appropriately functionalized [3]dendralenes have indeed been described very recently. Thus the benzylidene derivative **71** of acetylacetone **70** is easily transformed into the bisenol ether **72**[37,38].



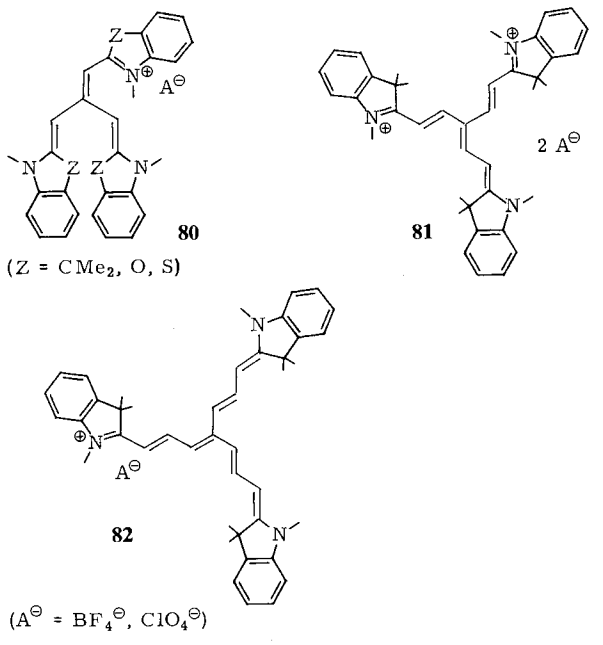
70 **71** **72** **73** **74** **75**

In Diels-Alder additions with double and triple bond dienophiles **72** functions as a double diene: initial Diels-Alder addition generates a new diene system in the 1:1-adduct **73**, which is capable of binding a second dienophile molecule. The resulting 2:1-adducts (here **74**) may not be stable under the addition conditions (aromatization to **75**); in any case, however, a highly functionalized product results. These so-called "diene-transmissive Diels-Alder reactions"[37,38] also occur in the reaction of **12** with maleic anhydride and quinones[16,17]; their designed use in organic synthesis is, however, of more recent origin[37,38]. Functionalized [3]dendralenes such as **78** and **79** are also obtained when alkylallenes, e.g. tetramethylallene **76**, react with electron-deficient acetylenes **77** (R=CF_3, CO_2CH_3, etc.) in an ene reaction (yields: 30—70%)[39,40].



76 **77** **78** **79**

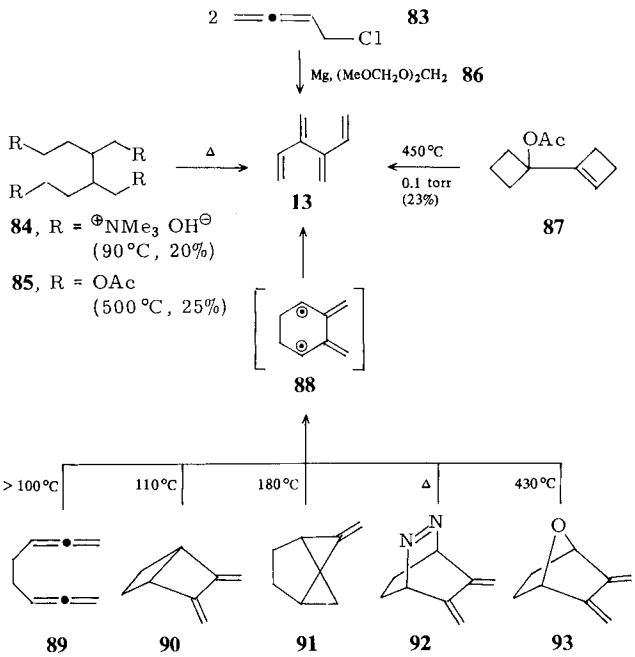
It should also be mentioned that cross-conjugation is a phenomenon widely known in dyestuff chemistry[41,42]. The numerous examples provided by di- and triarylcarbenium dyes and their aza-analogues as well as by many carbonyl dyes by far exceed the scope of this review. One example is the large number of (formal) derivatives of **12** among the trinuclear polymethyne dyes, e.g. the mono- and dications **80**—**82**, in which the π-electrons of the respective "dendralene parts" are delocalized over the entire system[43-45].



80 **81** **82**

2.2. 3,4-Dimethylene-1,5-hexadiene 13 ([4]Dendralene) and its Derivatives

For the preparation of **13** (Scheme 2), the methods that have already proven of value in the synthesis of **12** and its derivatives are used again (cf. Section 2.1). On the one hand, these are elimination reactions (**84** → **13**[46]; **85** → **13**[47]), which are easy to carry out, but require considerable synthetic effort to prepare the different substrates; on the other hand, thermal rearrangements are used that either start from isomeric allenes (**89** → **13**[48,49])

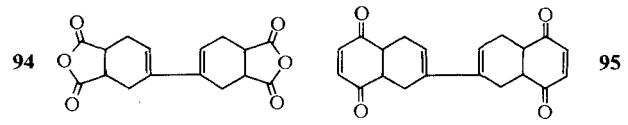


83 **86** **13** **87** **88** **89** **90** **91** **92** **93**

Scheme 2. Methods for the preparation of **13**.

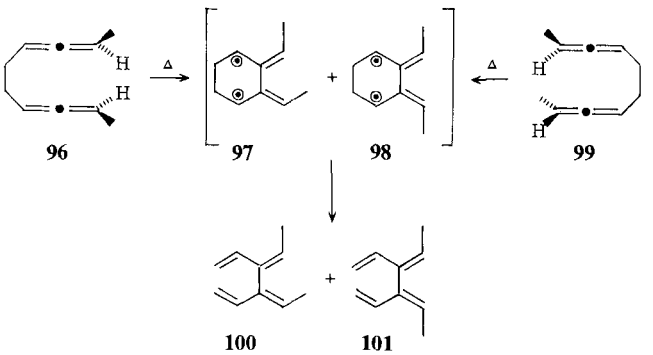
or strained ring compounds (**90** → **13**[49b,50]; **91** → **13**[49b,51]). Fragmentation of the bicyclic systems **92**[50] and **93**[49b] also provides **13**, which in these reactions is formed—in addition to other hydrocarbons—via the 2,3-dimethylene-1,4-cyclohexadiyl diradical **88**[52,53]. The synthesis of **13** from **87** proceeds via a combination of elimination and rearrangement[54]; this polyolefin is also obtained by oxidative dimerization of the Grignard reagent prepared from 1-chloro-2,3-butadiene **83** (Scheme 2)[55].

Although many methods are therefore known for the preparation of **13**, it must be pointed out that several of these do not satisfy preparative requirements. The chemical behavior of the polymerization-prone **13** remains largely unexplored. Cycloadditions with maleic anhydride and *p*-benzoquinone are claimed to yield the adducts **94** and **95**[46], i.e. the diene-transmissive Diels-Alder addition ceases at the 2:1-stage. Since the reactivity of the diene system in **94** and **95** (whose diketoform appears less likely) is not to be expected to be particularly low, these experiments should be repeated.



94 **95**

No designed syntheses of specifically substituted [4]dendralenes have been reported. *Skattebøl* and *Becher* isolated the diastereomeric dimethyl derivatives **100** and **101** on pyrolyzing *meso*- and (±)-2,3,7,8-decatetraene **96** and **99**, respectively. The composition of the product is independent of the configuration of the starting allene; the 1,4-diyls **97** and **98** have been proposed as reaction intermediates[56]. Alkyl derivatives of **13** are possibly also formed as side-products in the dimerization of α-bromoallenes with magnesium[57].

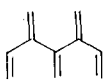


96 **97** **98** **99**

100 **101**

2.3. 3,4,5-Trimethylene-1,6-heptadiene 102 ([5]Dendralene)

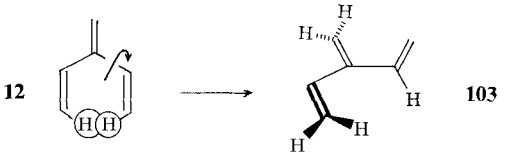
Like many other acyclic cross-conjugated polyenes, [5]dendralene **102** has been the subject of quantum mechanical calculations[58], although it has not been prepared so far. Even if **102** could be obtained by a preparatively simple route, it would presumably be difficult to study its chemical properties since it is probably a very reactive substance. As is frequently the case in hydrocarbon chemistry, polyalkyl or aryl substitution should lead to a marked decrease in reactivity.



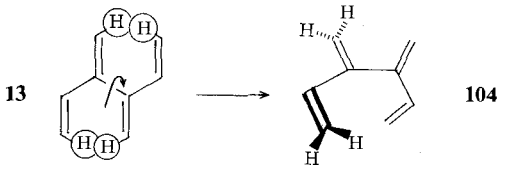
102

3. Cyclic Dendralenes

Astonishingly, the UV spectra of **12** (λ_{max} = 224 nm, $\log\varepsilon$ = 4.41)[16,17] and **13** (216.5 nm, 4.56)[46–48] hardly differ from that of 1,3-butadiene **4** (217 nm, 4.32)[59]. It is assumed that the nonplanarity of the dendralenes is responsible for this effect. As indicated by inspection of molecular models, planar structures for **12** and **13** would cause severe steric hindrance between the "*endo*"-hydrogen atoms. To avoid this accumulation of substituents, the polyenes prefer twisted conformations as shown in **103** and **104**, respectively. As a consequence, the *p*-orbitals can no longer assume the parallel alignment required for maximum overlap, and the absorption maxima are shifted to lower wavelengths. In order to study the spectroscopic and chemical properties of a planar dendralene, rotation about



12 **103**

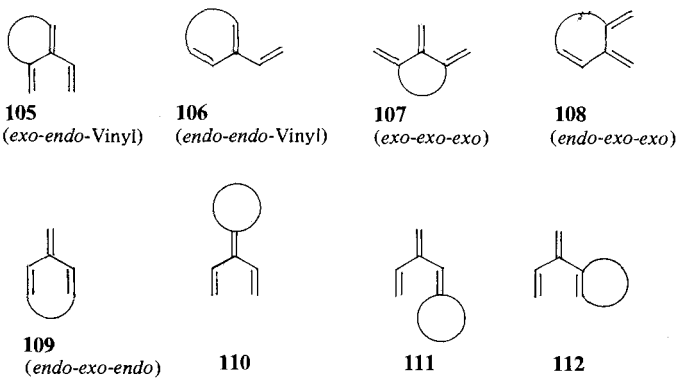


13 **104**

the single bonds must be prevented. This is accomplished most effectively by bridging, i.e. by incorporating the dendralene system into a cyclic molecule. The bridging permits only very specific arrangements of the double bonds and, hence, should also influence the chemical behavior of the various dendralenes.

3.1. Monocyclic [3]Dendralenes

If we disregard *E*/*Z*-isomers, [3]dendralene **12** may be bridged in eight different ways (Scheme 3). Whereas in types **105** and **106** the rotation about only one single



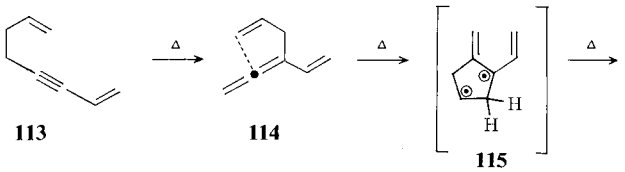
105 (*exo-endo*-Vinyl) **106** (*endo-endo*-Vinyl) **107** (*exo-exo-exo*) **108** (*endo-exo-exo*)

109 (*endo-exo-endo*) **110** **111** **112**

Scheme 3. Monocyclic [3]dendralenes.

bond is not possible, the dendralenes **107**—**109** are locked in a coplanar structure, especially with short molecular bridges. Systems **110**—**112** still possess "free" vinyl groups, but their rotational barriers should be higher than those of the parent compound **12**.

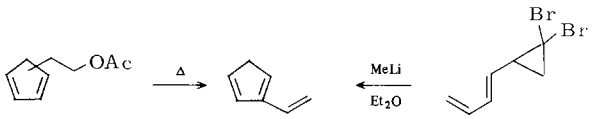
As shown in the following sections, representatives of practically all bridging types are known today, and thermal isomerizations again play a decisive role in their preparation (for types **110**—**112** no literature search was carried out). In a novel multi-step rearrangement which affords [3]dendralenes of the *exo,endo*-vinyl type **105**, 1,7-octadien-3-yne **113** undergoes thermal isomerization via a [3,3]sigmatropic rearrangement to give the (isolable) allene **114**, which via diradical **115** and 1,2-hydrogen shift stabilizes either to the dendralene **116** (44%) or to the triene **117** (52%)[27]. 6-Methyl derivatives of **113** lead to the expected methyl compounds **118**[60].



113 **114** **115**

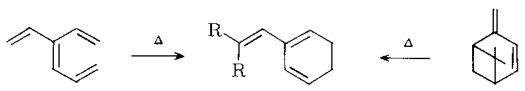
116 **117** **118a**, $R^1 = R^2 = CH_3$; **118b**, $R^1 = H$, $R^2 = CH_3$

Although the lower homologues of the *endo,endo*-vinyl series **106** are known, the lack of specificity makes the routes leading to them essentially worthless for practical purposes. Thus 2-vinyl-1,3-cyclopentadiene **120** is formed together with two dozen other hydrocarbons upon pyrolysis of the isomeric acetates **119**[61]. Treatment of the dibromocyclopropane **121** with an excess of methyllithium in ether at 0°C furnishes **120**, its 1-vinyl isomer, as well as 1,2,4,6-heptaetraene[62].



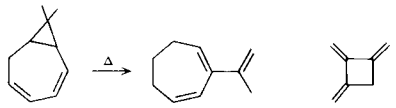
119 **120** **121**

The next higher homologue, **122a**, is obtained by electrocyclizing the vinyl [3]dendralene **53** (cf. Section 2.1), surprisingly, cyclization of 3-ethyl-1,3,5-hexatriene is 30 times slower[30].



53 **122a**, R = H; **122b**, R = CH_3 **123**

Compound **122a** has also been shown to be a decomposition product of **54**[31]. The 2-methyl-1-propenyl derivative of 1,3-cyclohexadiene **122b** is formed in 14% yield accompanied by three isomeric hydrocarbons upon gas phase pyrolysis of (+)-verbenene **123** at 390°C[63]. Thermal isomerization also affords the seven-membered ring compound **125** (pyrolysis of 8,8-dimethylbicyclo[5.1.0]octa-2,4-diene **124** at 250°C[64,65]).

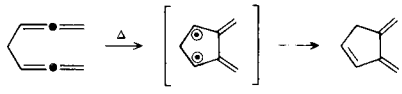


124 **125** **126**

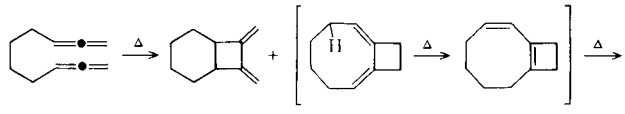
The only known representative of the *exo,exo,exo*-type **107** is 1,2,3-trismethylenecyclobutane **126**, prepared by conventional methods from cyclobutanetricarboxylic acid[66,67]. Isomers of the higher homologues have been described[3,4]; none, however, with three *exo*-methylene groups arranged consecutively.

For the synthesis of the *endo,exo,exo*-[3]dendralenes **108** allenic substrates or intermediates may again be employed. The parent hydrocarbon of this series, 3,4-bismethylenecyclopentene **129**, is obtained from 1,2,5,6-heptatetraene **127** by intramolecular cycloaddition via the diradical **128**[68]:

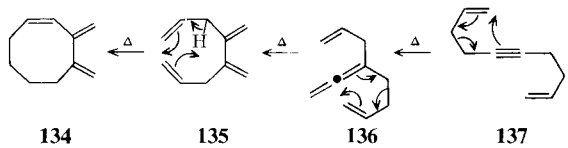
An analogous cycloaddition initiates the formation of 3,4-bismethylenecyclooctene **134**, which is isolated together with the cycloadduct **131** when **130** is pyrolyzed above 300°C[48,69]. The precursor of **134** could be the regioisomer **132**, which in turn could rearrange to **133** by 1,5-hydrogen shift. Under the pyrolysis conditions, the latter intermediate could undergo conrotatory ring opening to **134**. By means of on entire cascade of pericyclic reactions, **134** has recently been prepared from the acyclic trienyne **137**[70]: a tandem Cope rearrangement first produces 4,5-bismethylene-1,7-octadiene **135** via the (isolable) allene **136**; **135** is unstable under the pyrolysis conditions and cyclizes to **134** by an intramolecular ene-reaction[71].



127 **128** **129**

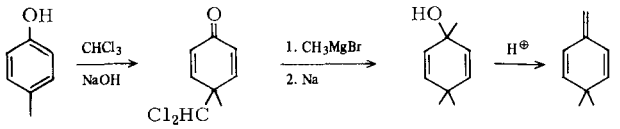


130 **131** **132** **133**



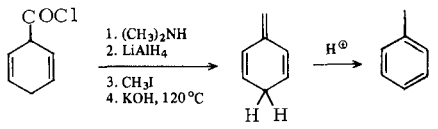
134 **135** **136** **137**

Of all known dendralenes, the *endo,exo,endo*-derivatives **109** are the most thoroughly studied. Derivatives of the lowest member of this homologous series were studied around the turn of the century by *Karl Auwers* et al. in the course of investigations on semibenzenes. As the most simple hydrocarbon, the 3,3-dimethyl compound **141** was obtained.



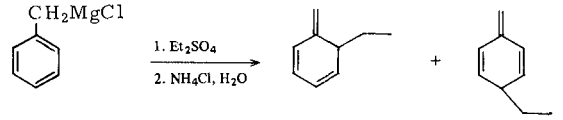
138 139 140 141

Under the conditions of the Reimer-Tiemann reaction *p*-cresol **138** affords the cyclohexadienone **139**, which was reduced by standard methods to the tertiary alcohol **140**. As expected, this is acid-sensitive and is readily dehydrated to **141**[72]. By a similar approach, semibenzenes with chlorine substituents in the nucleus were obtained[73]; *Auwers* et al. suspected that 3-methylene-1,4-cyclohexadienes bearing one or no substituents at the 6-position could not be prepared, since they would "presumably easily isomerize to benzene derivatives". This assumption was proven to be correct 60 years later by *Plieninger* and *Maier-Borst*, who first synthesized 3-methylene-1,4-cyclohexadiene **143** from 1,4-dihydrobenzoyl chloride **142**[74,75]. Traces of acid induce isomerization of **143** to toluene **144**. This so-called semibenzene rearrangement may also be initiated thermally, as shown with numerous derivatives of **143**[76–82].



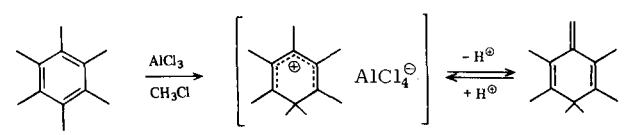
142 143 144

3-Methylene-1,4-cyclohexadienes monosubstituted in the 6-position, including the ethyl derivative **147**, are obtained when benzylmagnesium halides **145** are first alkylated and the reaction mixtures subsequently carefully hydrolyzed with saturated ammonium chloride solution[83]. Besides the dendralene, its linear conjugated isomer is produced, here **146** (**146** : **147** = 3 : 1)[84].



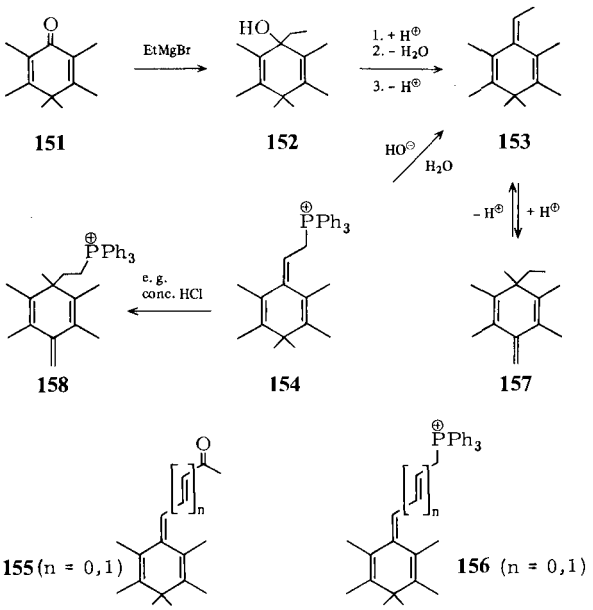
145 146 147

Polyalkylated derivatives of **143** (e.g. **150**) are, on the other hand, obtained via cationic intermediates by a method discovered by *Doering* et al.[85], and later generalized particularly by *Hünig* and *Schilling*[86]. In their most simple form, polyalkylbenzenes such as hexamethylbenzene **148** serve as substrates which are converted by Friedel-Crafts alkylation in an initial step into isolable σ-complexes **149** ("heptamethylbenzenium ion"). Rather than aromatizing to the starting material by loss of a methyl group, **149** loses a proton to generate the ring-permethylated hydrocarbon **150**. Its formation is reversible: aqueous hydrochloric acid suffices to establish the equilibrium **150** ⇄ **149**[85,88].



148 149 150

In the *Hünig* variant[86], **151** and **154** are employed as substrates for the ethylidene derivative **153**. On treatment with acid, **153** equilibrates with its isomer **157**, and **154** is correspondingly converted into the isomeric dendralene **158**. *Doering*'s triene **150** has been used as starting material for a whole series of vinylogous cross-conjugated systems[89]. The aldehydes **155** and phosphonium salts **156** are mentioned explicitly since certain bicyclic dendralenes with very extended π-systems (cf. Section 3.2) can be prepared from them.

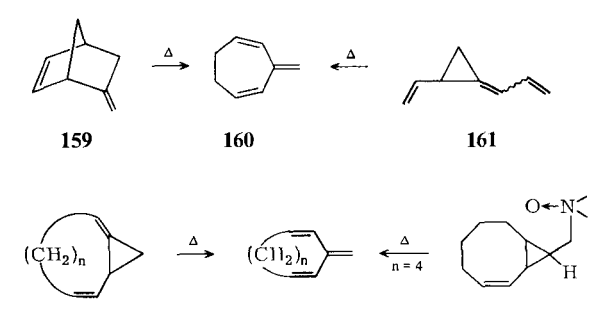


151 152 153 158 154 157

155 (n = 0,1) 156 (n = 0,1)

Apart from elimination reactions, the cyclic [3]dendralenes of type **109** have also been obtained by Wittig reaction from the corresponding cyclohexadienones[90,91].

The syntheses of the higher homologues of 3-methylene-1,4-cyclohexadiene **143** are again dominated by thermal processes: 3-methylene-1,4-cycloheptadiene **160** is formed—in low yield and accompanied by many other products—on gas-phase pyrolysis (670 °C, 3 torr) of 5-methylenebicyclo[2.2.1]hept-2-ene **159**[92] as well as by thermal isomerization of 1-allylidene-2-vinylcyclopropane **161**; 4-vinyl-3-methylenecyclopentene is formed as sole byproduct[93]. The 8- to 10-membered ring trienes **163** are



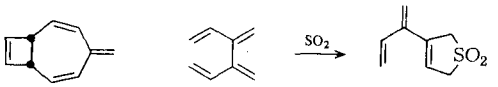
159 160 161

162 (n = 3-5) 163 (n = 3-5) 164

generated smoothly by pyrolysis of the bicycloalkadienes **162**[94,95]; alternatively 3-methylene-1,4-cyclononadiene has been obtained from **164** in 50% yield by Cope-elimination[96].

165, a bicyclic derivative of **160**, has been prepared by a similar route[96], and a 3,7-bismethylene-1,4-cyclooctadiene is described in Section 3.3[97].

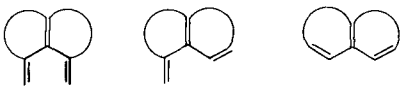
As a curiosity, it might be mentioned that the addition of sulfur dioxide to [4]dendralene **13** yields the sulfone **166** i.e. an example of the bridging type **112**[49c].



165 **13** **166**

3.2. Bicyclic [3]Dendralenes

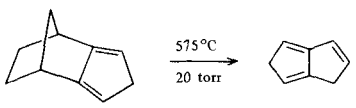
Not surprisingly, the number of ways of bridging a [3]dendralene increase rapidly when a second bridge is introduced. Altogether, 38 bicyclic molecular frameworks with a [3]dendralene subunit are conceivable, but of these, we will only deal with those molecules whose molecular bridges hold the triene in a coplanar arrangement. As shown by the (selected[98]) general structures **167**—**171**, the relative mutual orientation of the double bonds may be predetermined by the designed introduction of the bridge. This again makes the resulting polyenes interesting model substrates for spectroscopic and chemical studies.



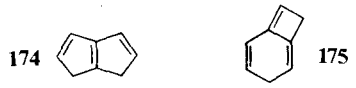
167 **168** **169**

170 **171**

At present, however, only very few of these structural types are accessible. The simplest bicyclic coplanar [3]dendralenes possess the molecular formula C_8H_8, i.e. these hydrocarbons must either be the bicyclo[3.3.0]trienes **173** and **174** or the bicyclo[4.2.0]octatriene **175**; with the last-mentioned most probably being a very highly strained and, therefore, extremely short-lived molecule.

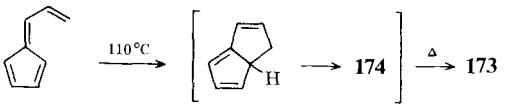


172 **173**



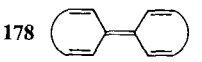
174 **175**

Of the two dihydropentalenes **173** and **174**, *Katz* and *Rosenberger* generated **173** by gas-phase pyrolysis of isodicyclopentadiene **172**; **173** was used for the first synthesis of the pentalenyl dianion[99]. In a remarkable isomerization described by *Gajewski* and *Cavender*, 6-vinylfulvene **176** is connected via **177** and **174** to **173**[100].

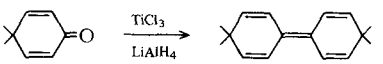


176 **177**

Analogously, 6-propenylfulvene rearranges to methyl derivatives of **173**[100]. A third route to **173** involves flow pyrolysis (400—665 °C) of cyclooctatetraene, with the semibullvalenyl diradical as the most probable intermediate[101]. Six-membered ring trienes of the types **167**—**171** have, as for as I know, not yet been described. These compounds should aromatize easily, as has been observed for 1,3- and 1,4-cyclohexadiene under relatively mild conditions[102]. In the case of condensed cyclobutene rings, (thermal) ring-opening is to be expected.



178



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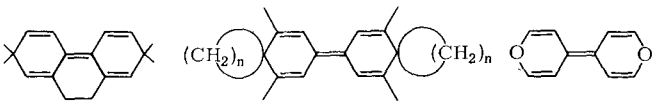
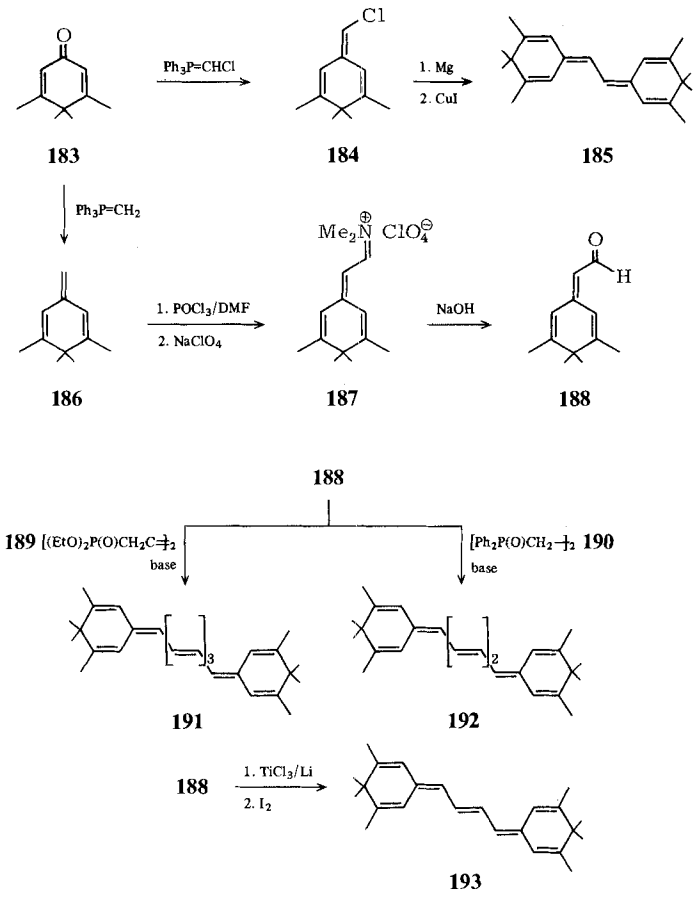


180 **181a**, n = 4 **182**
181b, n = 5

178, which may be regarded as a doubly bridged derivative of **61** (cf. Section 2.1), is a special bicyclic polyene with cross-conjugated double bonds. The first hydrocarbon of this type, 4,4,4′,4′-tetramethylbi(2,5-cyclohexadienylidene) **179** was prepared by *Lüttke* and *Janssen* by a simple and effective method[103]: McMurry coupling[104] of a dimethyl derivative of the ketone **139**, which had already been used for the preparation of **141**, gave the pentaene **179** in 97% yield. Comparable procedures lead to some derivatives of **179**, among them **180**[103], **181a**, **b**[105], and **182**[103,106]. Structurally and spectroscopically **179** belongs to the most carefully and widely studied cross-conjugated polyolefins yet known[107a-e].

Hünig et al. have used dendralenic substrates to prepare vinylogous derivatives of **179**[89,105], and Scheme 4 presents some characteristic examples of their extensive work[108].

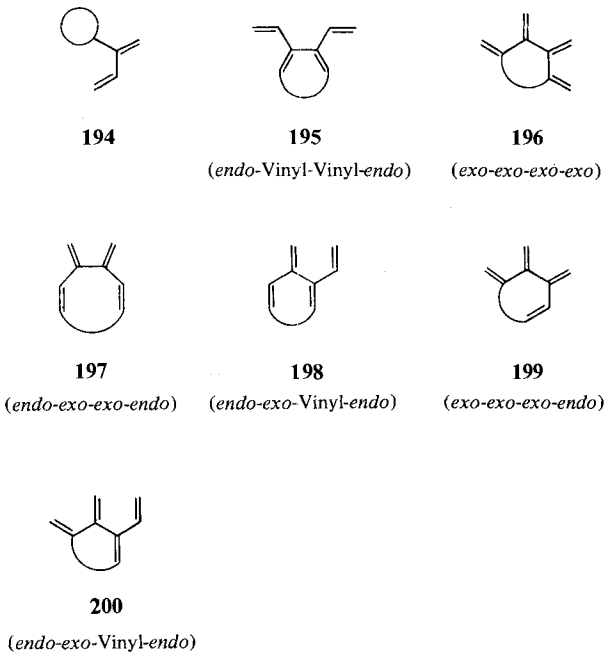
Key intermediate in this reaction is the cross-conjugated dienone **183** which can be olefinated to **186** or to its chloro derivative **184**, as desired. Reductive coupling of the triene **184** leads to **185**, whereas **186** can be readily converted into the aldehyde **188**, a second key compound, via the Vilsmeier salt **187**. Double Wittig reaction with the ylides of **189** and **190** furnishes **191** and **192**, respectively, and McMurry coupling of **188** finally yields **193**.



Scheme 4. Synthesis of extended cross-conjugated polyenes from monocyclic [3]dendralenes. DMF = dimethylformamide.

3.3. Mono- and Bicyclic [4]Dendralenes

[4]Dendralene **13** may be incorporated into a monocyclic ring system in eleven ways. If all structures still possessing a "free" butadienyl group (**194**) are neglected, six arrangements **195**–**200** remain whose double bond systems are sterically more or less fixed.



194

195 (*endo*-Vinyl-Vinyl-*endo*)

196 (*exo-exo-exo-exo*)

197 (*endo-exo-exo-endo*)

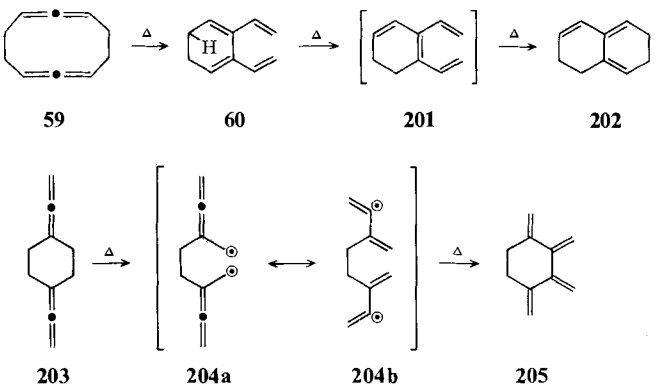
198 (*endo-exo*-Vinyl-*endo*)

199 (*exo-exo-exo-endo*)

200 (*endo-exo*-Vinyl-*endo*)

The first compounds of these structural types have been prepared recently, and thermal rearrangements of allenes again play a decisive role in their preparation.

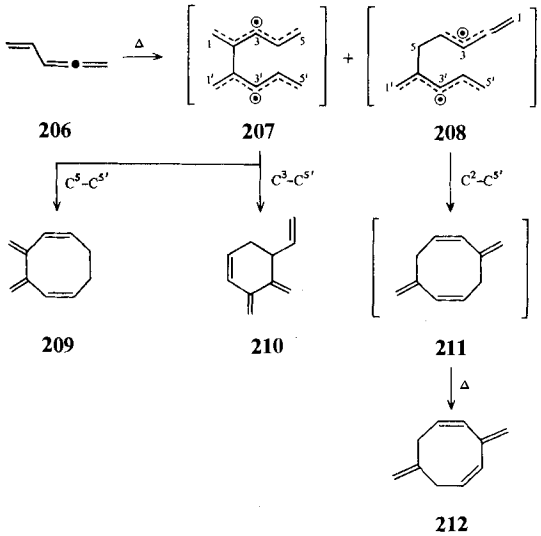
The isomerization (300 °C, gas phase) of 1,2,6,7-cyclodecatetraene **59** to 2,3-divinyl-1,3-cyclohexadiene **60** has already been mentioned[48] (see Section 2.1). At higher temperatures **60** is unstable and isomerizes by a 1,5-hydrogen shift via **201** and its electrocyclic ring closure to **202**, i.e. it is converted into a bicyclic [3]dendralene of type **170**[109]. Hydrocarbon **203**, an isomer of **59** with two exocyclic allene groups, isomerizes upon gas-phase pyrolysis (500 °C, 0.1 torr) to afford a monocyclic [4]dendralene, 1,2,3,4-tetramethylenecyclohexane **205**[110]. The most likely primary intermediate in this process is the diradical **204a,b**, which recyclizes in surprisingly high yield (82%).



59 **60** **201** **202**

203 **204a** **204b** **205**

Three different cross-conjugated monocycles are produced—in addition to three other dimers—when 1,2,4-pentatriene **206** (vinylallene) is heated to 170 °C[97]. The



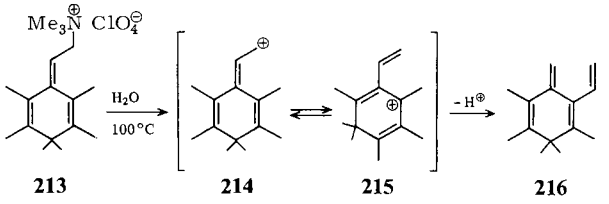
206 **207** **208**

209 **210** **211**

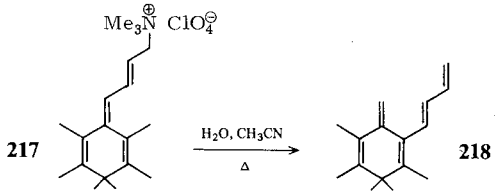
212

formation of the monocyclic [4]dendralene **209** (25%, GC-analysis) by C^5–$C^{5'}$ coupling of the diradical **207** competes with formation of the [3]dendralenes **210** (19%; type **107**) and **212** (5%; type **108**). Whereas **207** also serves as a precursor of the six-membered ring compound (C^3–$C^{5'}$ coupling), **212** is preceded by the isomeric tetraolefin **211**. This last-mentioned compound should arise from diradical **208** by C^2–$C^{5'}$ coupling and rearranges under the pyrolysis conditions via 1,3-hydrogen shift to the final product[97].

A partially coplanar [4]dendralene of type **198**, the pentamethyl derivative **216**, was obtained by *Hünig* and *Schilling* by hydrolysis of the perchlorate **213**. Primary intermediate is the cation **214**, which isomerizes to the more stable **215**; deprotonation subsequently provides the tetraene **216**. Likewise, the vinylogous salt **217** is converted into the cross-conjugated pentaene **218** (major product[86]).



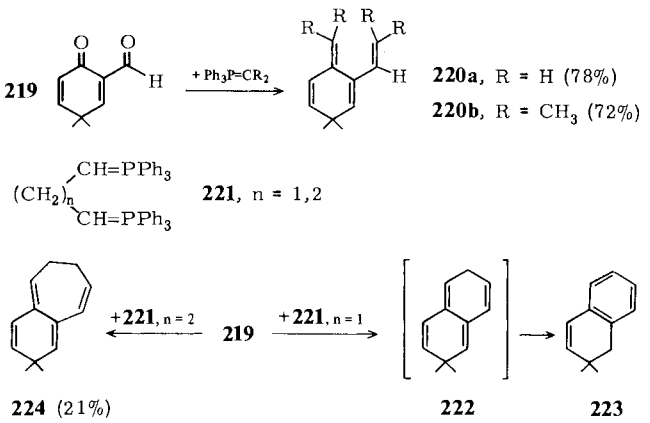
213 **214** **215** **216**



217 **218**

The Wittig reaction may also be employed for the synthesis of derivatives of **198** and **216**, as shown by *Cassens* and *Lüttke*[111].

Key intermediate in this instance is 2-formyl-4,4-dimethylcyclohexadienone **219**, a cross-conjugated molecule. With simple ylides it is olefinated readily to the tetraenes **220**, but with the bisylide **221** (n = 1) instead of **222** its



isomerization product **223** is obtained. In view of the high tendency of 3-methylene-1,4-cyclohexadienes to aromatize (see Section 3.1), this result comes as no surprise. With **221** (n = 2), however, the first doubly-bridged [4]dendralene, 9,9-dimethylbicyclo[5.4.0]undeca-1,5,7,10-tetraene **224**, is isolated. Its spectroscopic data clearly show that this hydrocarbon is indeed a coplanar [4]dendralene[111].

4. Concluding Remarks and Outlook

It was the purpose of this review to collect for the first time the widely scattered experimental material on the synthesis of cross-conjugated polyenes of the dendralene type. That at least one hundred compounds of this type are known seems at first sight to contradict the title of this article; nevertheless, it is justified and does not even require a question mark.

Neglected so far have been comprehensive and comparative studies on the chemical behavior of the dendralenes, which more often than not were obtained more or less serendipitously in various chemical transformations rather than by carefully planned syntheses. Like all olefinic π-systems, the dendralenes are suitable educts for addition reactions of all types; the Diels-Alder addition discussed above illustrate this[112]. The thermal and photochemical behavior of these hydrocarbons ought also to be studied, as should their possible application as ligands for novel metal complexes. A systematic attempt to broaden the experimental basis via carbocations[113, 114] and carbanions[115] derived from the simple cross-conjugated hydrocarbons would be welcome. These ions very probably possess interesting spectroscopic properties, and may be valuable for the introduction of preparatively useful functional groups[116].

Dendralenes with sterically fixed structures are interesting objects for spectroscopic studies, as shown very recently by the investigations of *Lüttke* et al.[107, 111]. But more attention should also be given to the spectroscopic and structural properties of the acyclic dendralenes. It has, for example, up to now not been verified experimentally whether [3]dendralene **12** really possesses the "twisted" structure suggested by formula **103** (and several theoretical calculations[111]). In fact, the numerous theoretical studies on the electronic structure and bonding properties of cross-conjugated hydrocarbons should be confirmed by experimental work.

For our own work reported in this review, I would like to thank my co-workers whose names appear in the appropriate references. Their interest and experimental expertise made this work possible, under conditions often far from ideal. For literature references and helpful discussions I would like to thank Professors S. Hünig (Würzburg), M. Neuenschwander (Bern), the Dozenten W. Grahn (Braunschweig), H. Hauptmann (Regensburg), and especially Professor W. Lüttke (Göttingen); without the many discussions I had with him on hydrocarbons (and other matters), this review would probably not have been written. For permanent and generous support of our work on highly unsaturated hydrocarbons I am very grateful to the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie as well as to BASF, Bayer, Hoechst, Degussa, and Metallgesellschaft.

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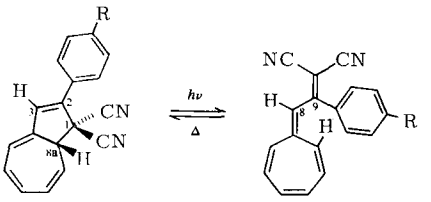
Photosensitive Dihydroazulenes with Chromogenic Properties**

By *Jörg Daub**, *Thomas Knöchel*, and *Albrecht Mannschreck*

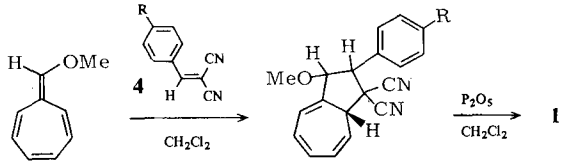
Compounds having photochromic and thermochromic properties are useful for solar energy conversion and for information storage[1]. In the case of organic compounds, this behavior is often associated with reversible valence isomerizations. For instance, the pair of compounds norbornadiene/quadricyclane have been exhaustively examined regarding their use in energy conversion[2]. In the following communication it is shown that the "ten-electron reaction" between the dihydroazulene **1** and the 8-vinylheptafulvene **2** can be driven thermally in the direction **2**→**1**, and by daylight in the direction **1**→**2**. This reaction behavior, which very strongly depends on the aryl groups at C-2 and C-9, in the compounds **1** and **2**, respectively, could find application in information storage[3].



1 **2**

a, R = OCH_3; **b**, R = NO_2

The dihydroazulenes **1**[6] were prepared from 8-methoxyheptafulvene **3**[4] and the dicyanoethylenes **4**. [8+2]-Cycloaddition leads regiospecifically and quantitatively to **5**.



3 **5**

a, R = OCH_3; **b**, R = NO_2

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Both **5a** as well as **5b** are formed as diastereomeric mixtures[5,6]. The double bond between C-2 and C-3 is introduced by elimination of methanol with phosphorus pentoxide. In **1** the bond between C-1 and C-8a is thermally stable in solution at room temperature. To prove this, (+)-**1a** and (−)-**1a** were enriched by liquid chromatography on swollen triacetylcellulose[7] in the absence of light[8]. Ethanolic solutions of the enantiomers do not racemize in the dark.

In contrast, the yellow solutions of **1** turn dark-red on exposure to daylight. **1a** reacts more rapidly than **1b**. For instance, Figure 1 shows the change in the UV/VIS spectrum of **1a**. It was demonstrated by ^{1}H-NMR spectroscopy that **1a** is converted exclusively and completely into **2a** on irradiation (sunlight or Osram HWLS 500 W electric bulb)[6]. **2a** remains unaltered, even on prolonged irradiation (44 h). **1b** behaves differently: The exposure to light leads not only to **2b**[6], but also to secondary products which manifest themselves in the electronic spectrum by new bands at 260, 295, and 315 nm, while the characteristic bands (483 nm for **2b** and 385 nm for **1b**) disappear on prolonged irradiation.

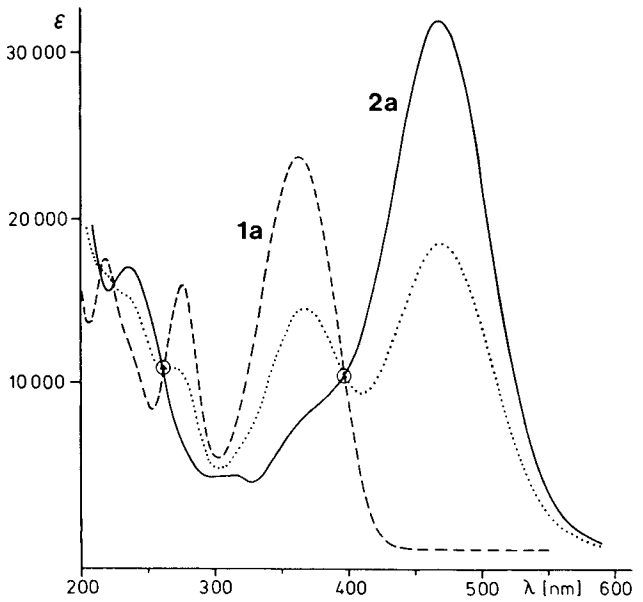

Fig. 1. Photochemistry of **1a** in acetonitrile ($c = 4.9 \times 10^{-5}$ mol/L), irradiation by daylight. (---) Start, (....) after 1 min, (—) after 7 min.

According to the spectroscopic data, the compounds which are formed in the photochemical conversions of **1** and which are found to absorb at long wavelengths have the heptafulvene structure **2**[6,9]. Characteristic for **2** are the strong-intensity bands of the nitrile groups at 2220 cm^{-1} in the IR spectrum and the absorptions at $\lambda = 467$ nm for **2a** and 483 nm for **2b**. Consistent with this are also changes in the chiroptic properties. For example, when a solution of (+)-**1a** in acetonitrile is exposed to daylight, the bands at 220 nm ($\Delta\varepsilon = +6.5$ L·mol^{-1}·cm^{-1}), 275 nm ($\Delta\varepsilon = -6.9$ L·mol^{-1}·cm^{-1}) and 365 nm ($\Delta\varepsilon = +1.7$ L·mol^{-1} cm^{-1}) in the CD spectrum disappear[10].

On the other hand, the heptafulvenes **2** are thermolabile. In the dark, **2a** ($c = 5 \times 10^{-5}$ mol/L in CH_3CN) rearranges quantitatively within 70 h at 25 °C into **1a**. Under the same conditions, this electrocyclic ring closure requires 16 h in the case of **2b**; the formation of a by-product with UV/VIS bands at 315 nm can also be observed in this reaction. In contrast to **1b**/**2b**, the chemical oscillation between **1a** and **2a** proceeds without any losses, even on prolonged reaction. Thus, no decrease in extinction was observed, even after 15 oscillations at room temperature.

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[6] **5a**: Colorless crystals, m.p. 119–124 °C; IR (KBr): $\tilde{\nu}$ = 2250, 1605, 1505 cm^{-1}; ^{1}H-NMR (main product, 60 MHz, $CDCl_3$): δ = 3.20 (m; 1H, 8a-H), 3.25 (s; 3H, OCH_3), 3.70 (d, J = 3.8 Hz; 1H, 2-H), 3.88 (s; 3H, Aryl-OCH_3), 4.35 (d, J = 3.8 Hz; 1H, 3-H), 5.72 (dd, J = 9.4 Hz, J = 4.0 Hz; 1H, 8-H), 6.15–6.84 (m; 4H, 4-H to 7-H), 7.00 and 7.73 (Aryl-H).—**5b** [5].—**1a**: Lemon yellow crystals, m.p. 125–126 °C (MeOH); IR (KBr): $\tilde{\nu}$ = 1605, 1585 cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 3.77 (m; 1H, 8a-H), 3.86 (s; 3H, OCH_3), 5.81 (dd, J = 10.3 Hz, J = 3.8 Hz; 1H, 8-H), 6.29 (m; 2H, 4-H, 7-H), 6.44 (dd, J = 10.5 Hz, J = 6.0 Hz; 1H, 5-H), 6.55 (m, J = 10.5 Hz, J = 6.3 Hz, J = 0.8 Hz; 1H, 6-H), 6.76 (s; 1H, 3-H), 6.99 and 7.67 (Aryl-H); UV (CH_3CN): λ_{max} (log ε) = 365 (4.4), 275 (4.2), 220 (4.2) nm.—**1b**: yellow crystals, m.p. 145–146 °C (MeOH); IR (KBr): $\tilde{\nu}$ = 1580, 1570, 1330 cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 3.84 (m; 1H, 8a-H), 5.83 (dd, J = 10.3 Hz, J = 3.8 Hz; 1H, 8-H), 6.35 (m; 1H, 7-H), 6.56 (m; 3H, 4-H, 5-H, 6-H), 7.07 (s; 1H, 3-H), 7.90 and 8.33 (Aryl-H); UV (CH_3CN): λ_{max} (log ε) = 385 (4.2), 235 (4.0) nm.—**2a**: IR ($CHCl_3$): $\tilde{\nu}$ = 2850, 2220, 1605 cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 3.87 (s; 3H, OCH_3); 5.94, 6.30, 6.70 (m; 6H, fulvene-H), 6.27 (s; 1H, 8-H), 6.97 and 7.38 (Aryl-H); UV (CH_3CN): λ_{max} (log ε) = 467 (4.5), 237 (4.2) nm.—**2b** was not isolated but merely enriched in the respective solutions used for the measurements: IR ($CDCl_3$): $\tilde{\nu}$ = 2220, 1710 cm^{-1}; UV (CH_3CN): λ_{max} (log ε) = 483 (4.1).

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Chemoenzymatic Synthesis of a Functional Gene for Human Gamma Interferon**

By *Joachim Engels**, *Michael Leineweber,* and *Eugen Uhlmann*

Gamma interferon (γ-IFN), previously called immune interferon, is a lymphokine having important antiproliferative and immunoregulatory properties[1]. In 1982, two research groups[2,3] working independently of each other succeeded in deriving the primary structure of γ-IFN from its gene sequence. The gene was then incorporated and expressed in bacteria. If the amino acid sequence of a protein is known, chemoenzymatic gene synthesis offers the following advantages over the biochemical DNA isolation from biological material: 1) The frequently very difficult step of isolating the relevant mRNA or genomic DNA is avoided. 2) The desired DNA sequence is obtained directly without additional "tailoring" or processing of the isolated DNA. 3) Those codons, which code highly expressed pro-

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teins in the respective host organisms, can be used. 4) Later modifications of genes, be it shortening or lengthening, are easily made possible by introducing appropriate cleavage sites for restriction enzymes. Consequently, structure-activity studies can even be extended to relatively large peptides.

Based on the genetic code, we derived a DNA sequence coding for 146 amino acids of gamma interferon. We then selected codons of proteins which are highly expressed in *E. coli,* introduced suitable restriction enzyme cutting sites and avoided unnecessary symmetries or redundancies within the DNA sequence. In addition to the 146 coding nucleotide triplets, a start codon was attached at the 5′-terminal as well as two translation stop codons at the 3′-terminal. To this are attached the recognition sites for the restriction endonucleases *Eco*RI and *Sal*I. The whole gene, consisting of 452 base pairs was divided into three subunits, **IFN-I**, **IFN-II**, and **IFN-III** (Fig. 1), whose ends carry recognition sequences for restriction enzymes which otherwise are not present in the gene and which enable insertion into the plasmids in the desired orientation. The advantage of the subcloning principle, in which our synthetic strategy differs from the earlier gene syntheses[4,5], is that one-pot ligation steps are easily performable. Accordingly, cloning in *E. coli* and reisolation leads to a purification of the subfragments, whose sequences are confirmed by analysis. In earlier gene syntheses, mutated gene intermediates could only be separated with difficulty, if at all, since physical methods of purification were used. By subcloning, on the one hand the frequency of mutation in the whole gene is reduced and, on the other, an almost inexhaustable reservoir of the respective subfragments is available for subsequent alteration of the gene.

The subfragments were cut retrosynthetically into oligonucleotides in such a way (18 to 33 nucleotides) that overlapping sequences of six base pairs are present at the linkage points. The requisite 34 oligonucleotides were synthesized by the phosphoramidite method on solid phase as described by *Caruthers* et al.[6] and the crude products then purified by electrophoresis on polyacrylamide gel or by HPLC (C18 reversed phase or ion-exchange (Partisil SAX)). The oligonucleotides Ia—IIl were obtained as 5′-hydroxy compounds. Hence, the oligomers Ib—Ii, IIb—IIk, and IIIb—IIIk to be coupled at both termini were phosphorylated at the 5′-terminal with adenosine triphosphate and T4-polynucleotide kinase. For the enzymatic linkage, 1 nmol each of the oligomers Ia—Ij was heated in aqueous solution for 5 min at 90°C and then slowly (2—3 h) cooled to 16°C in order to achieve a hybridization to the DNA double strand. After addition of the enzyme polynucleotide ligase the solution was incubated for 18 h at 16°C and the subfragment **IFN-I** thus formed was isolated by electrophoresis on polyacrylamide gel. In the same way, the subfragments **IFN-II** and **IFN-III** were also prepared from the oligonucleotides IIa—IIl and IIIa—IIIl, respectively. After the subcloning of the gene fragments in suitable plasmids, an inexhaustable source of these fragments was available, since, after cleavage they could be reisolated with the restriction enzymes *Eco*RI and *Bam*HI from **IFN-I**, with *Bam*HI and *Hind*III from **IFN-II**, and with *Hind*III and *Sal*I from **IFN-III**. In each case the DNA sequence was verified by sequencing[7].

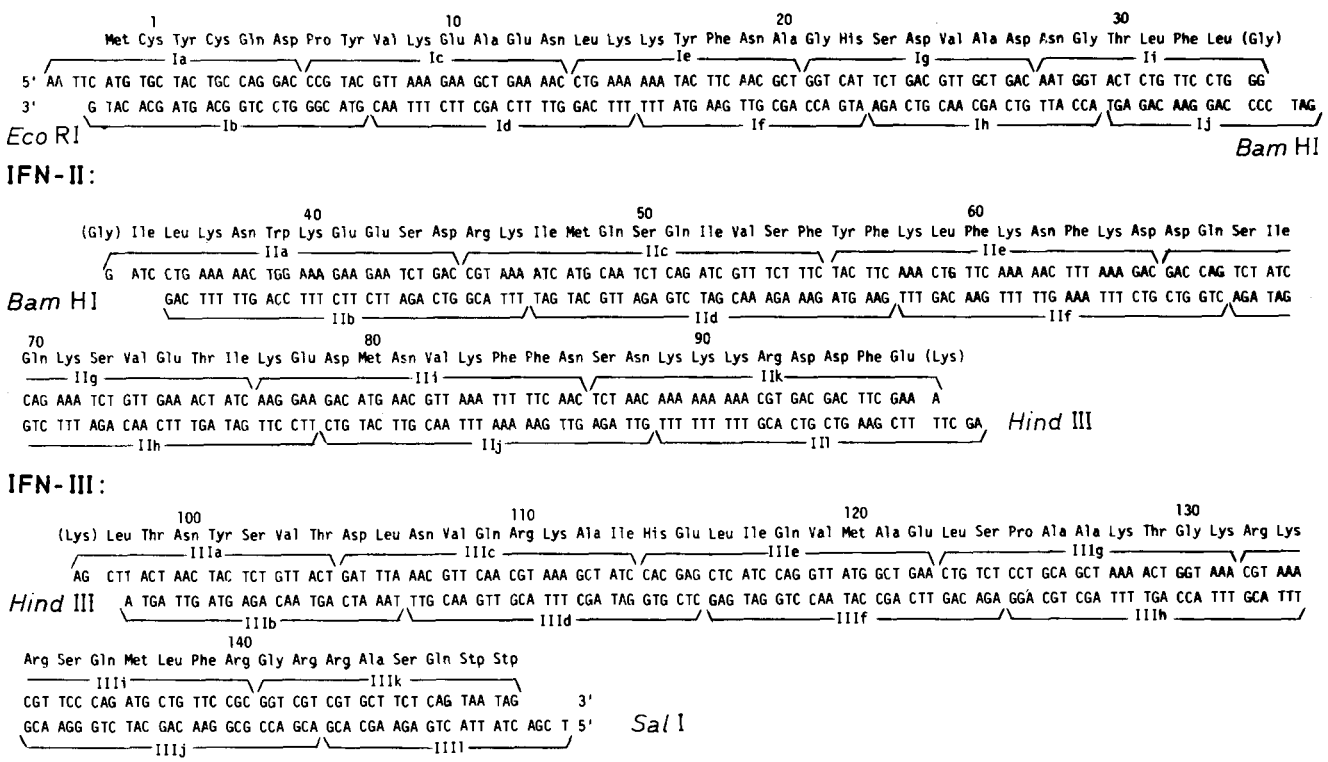

Fig. 1. Amino acid and nucleotide sequences of the synthetic human gamma interferon. The synthetic oligonucleotides Ia—IIl are bracketed. The numbering of the amino acids shows the native human γ-IFN sequence. For the synthesis of the oligonucleotides Ia—IIl, in each case 1 μmol of the 5′-OH nucleoside bonded via the 3′-hydroxy group on controlled pore glass (cpg) was allowed to react with 10 μmol 5′-*O*-dimethoxytritylnucleoside-3′-phosphoramidite and 50 μmol tetrazole in acetonitrile. After the capping of unreacted 5′-OH components with acetic anhydride/4-dimethylaminopyridine in tetrahydrofuran (THF), the internucleotidic phosphite ester was oxidized with I_2 in collidine/water/THF. For further lengthening of the chain the 5′-*O*-dimethoxytrityl group then had to be cleaved off with 3% trichloroacetic acid in 1,2-dichloroethane (w/v). The oligonucleotides were purified by polyacrylamide gel electrophoresis (15% polyacrylamide, 7 M urea) and, after elution from the gel, desalted on a Sephadex G50 column.

The gene fragments were ligated with the aid of polynucleotide ligase to form the complete gene (Fig. 2), which was then inserted into a plasmid opened with *Eco*RI and

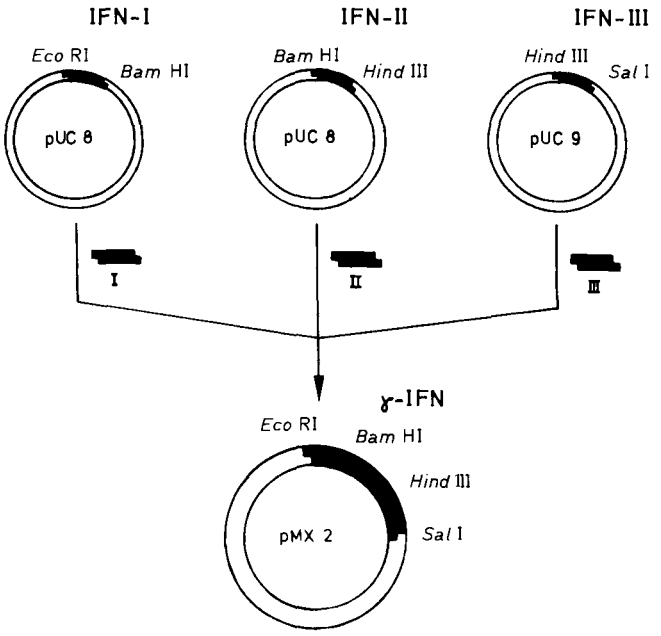

Fig. 2. Cloning vectors pUC8 and pUC9 with the gene fragments **IFN-I—IFN-III** and expression vectors pMX2 with the tac-regulation unit. For the construction of the expression vector pMX2 the gene fragments **IFN-I—IFN-III** were first subcloned in pUC8 and pUC9, respectively, as follows: 1 μg of the pUC plasmid (BRL, Neu-Isenberg) was digested with 2 to 5 units of the desired restriction endonucleases at 37 °C for 2 h in a buffer according to the manufacturers instructions. The back-bone plasmid was then separated from the cleaved oligonucleotides by electrophoresis on a 0.7% low melting point agarose gel. After cutting out the desired bands, melting the gel at 60 °C, phenol and ether extraction of the aqueous phase, the plasmid-DNA was isolated by precipitation with ethanol. 0.1 μg of the opened plasmid was subsequently ligated with 0.2 μg of the respective synthetic DNA fragment with the aid of 10 units T4-DNA-ligase at 4 °C for ca. 15 h and transformed by the usual $CaCl_2$-method in *E. coli* 7902. Clones with hybrid plasmids were worked-up according to a rapid lysate-method by treatment with alkali [9] and analyzed on the basis of the restriction enzyme cleavage pattern on 10% agarose gels. The gene fragments **IFN-I—IFN-III** were cleaved from the pUC vectors with the respective restriction endonucleases, reisolated by electroelution, phenol extracted, and precipitated with ethanol. The correctness of the two DNA strands was verified by sequencing according to the method of *Maxam* and *Gilbert* [7]. The total gene for γ-IFN was then obtained by ligation of the three gene fragments **IFN-I**, **IFN-II**, and **IFN-III** and once again incorporated into an expression plasmid "downstream" from the control region (trp-lac fusion promotor, lac-operator) [8], in the same way as described for the subfragments.

*Sal*I directly behind an expression regulation unit (tac-promotor[8]). After transformation and cloning in *E. coli* we were able to verify the correctness of the whole gene by restriction enzyme mapping and total sequencing according to the method of *Maxam* and *Gilbert*[7]. For the expression of the human gamma interferon gene, transformed cells of *E. coli* 7902 were cultivated in a shaking culture up to an optical density of 1 at 578 nm. The synthesis of the gamma interferon was then induced for 2 h by addition of isopropyl-β-D-thiogalactoside (IPTG; 10^{-3} M). After harvesting the cells by centrifugation and subsequent cell lysis by treatment with lysozyme/EDTA, the gamma interferon titers obtained in the cell residues were determined both by a specific radioimmunoassay for human gamma interferon (Celltech, Slough, UK) as well as by a biological test of the protective effect of the gamma interferon against a viral infection (vesicular stomatitis virus) in the case of vero cells. Induced cultures exhibit interferon titers of 1 mg per liter and OD (optical density unity at 578 nm), whereas non-induced cultures produced only 0.01 mg gamma interferon per liter and OD. The interferon-containing residues were finally purified with monoclonal antibodies (Celltech) bound to affinity columns. The fraction specifically bound by the antibodies were analyzed on SDS polyacrylamide gels. The observed protein bands corresponded to a protein with a molecular weight of about 16000 (molecular weight of γ-IFN).

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Second Order Jahn-Teller Effect in Hexahalogenotellurates(IV): Statically Distorted Anion in $Ca(H_2O,HF)_7TeBr_6$**

By *Walter Abriel** and *Hartmut Ehrhardt*

According to the VEPA theory[1], a distorted octahedral coordination is expected for systems of the type AX_6E (six bonding electron pairs, one nonbonding electron pair in the valence shell of the central atom). In the case of XeF_6 this can be detected in the gas phase, but the deformed species oscillates between energetically equivalent configurations (dynamic second order Jahn-Teller effect)[2,3]. According to the initial X-ray structure analyses (293 K) the analogous anions $TeX_6^{2\ominus}$ (X = Cl, Br, I), containing 14-electron systems, showed a regular octahedral structure[4]; consequently *Gillespie* classified these systems as exceptions to the rule[5].

The IR-active vibrations T_{1u} (ν_3 and ν_4) of the $TeX_6^{2\ominus}$ octahedron are, however, relatively broad; an indication of vibronic couplings between the ground state (configuration $a_{1g}\sigma^*$) and the first excited state (configuration $a_{1g}\sigma^*$, $t_{1u}\sigma^*$)[6]. Expectations of detecting a distorted species by X-ray structure analyses at temperatures up to 12 K were, however, not fulfilled in investigations on Rb_2TeBr_6[7]. As *Pearson*[2] presumed, the octahedrally enforced, dynamic structure is stabilized by a highly symmetrical crystal field,

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which, e.g., is realized in the A_2TeX_6 phases (A = K, NH_4, Rb, Cs; X = Cl, Br, I)[8] by an anti-fluorite arrangement of the cations and anions.

The transition from the dynamically distorted structure of the $TeBr_6^{2\ominus}$ ion to the statically distorted species is now described for the first time. This transition is achieved, on the one hand, by the lowering of the symmetry of the crystal field and, on the other, by the substitution of two monovalent cations by a stronger polarizing bivalent cation. Figure 1 shows the relevant IR absorption bands for the $TeBr_6^{2\ominus}$ ion[9]. The T_{1u} deformation vibrations (ν_3 and ν_4) for the cubic ($Fm\bar{3}m$) phase Rb_2TeBr_6 are reproduced in Figure 1a. In the case of $[Na(H_2O)_3]_2TeBr_6$ (a compound with monoclinic (C2/m) crystal structure, but according to the X-ray structure analysis with a regular octahedral anion[10]) a shoulder can be detected on the ν_4 bands as a result of the strongly anisotropic crystal field (Fig. 1b). Compared to the bands in the Figures 1a and 1b (dynamic distortion), which are already broad, in the spectra of the new compounds $Ca(H_2O,HF)_7TeBr_6$ and $Ca(H_2O)_7TeBr_6$ (Figs. 1c and 1d[11]) a further broadening with marked triple splitting occurs; in the case of the pure hydrate $Ca(H_2O)_7TeBr_6$ (Fig. 1d) the ν_3 band is shifted towards the blue region compared to that of $Ca(H_2O,HF)_7TeBr_6$ (Fig. 1c) because of the strong crystal field (smaller volume of the unit cell[12]). The splitting pattern is consistent with the point symmetry mm2 (C_{2v}).

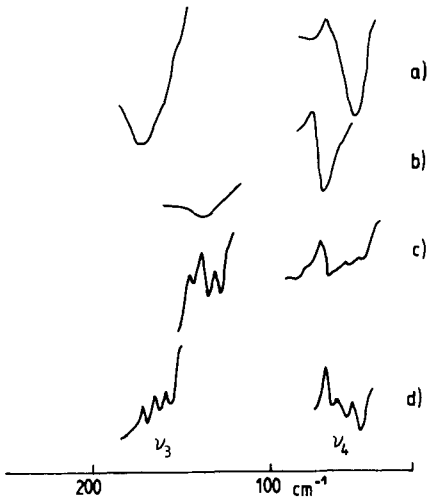

Fig. 1. FIR spectra of a) Rb_2TeBr_6, b) $[Na(H_2O)_3]_2TeBr_6$, c) $Ca(H_2O,HF)_7TeBr_6$, and d) $Ca(H_2O)_7TeBr_6$; for details see text.

The static distortion of the $TeBr_6^{2\ominus}$ ion could be detected by a single crystal X-ray structure analysis on $Ca(H_2O,HF)_7TeBr_6$[12], thus confirming the symmetry deduced from the vibration spectra (Fig. 2). The packing of the $Ca^{2\oplus}$ and $TeBr_6^{2\ominus}$ ions (Fig. 3) resembles that observed in the scheelite structure (e.g. $CaWO_4$[13]) regarding the ionic centroids.

The threefold degenerated T_{1u} deformation vibration of the octahedron, which alone can effect the above-mentioned vibronic coupling, has three independent components. These point to a distorted structure, resulting in the symmetries 4mm (C_{4v}), 3m (C_{3v}), and mm2 (C_{2v})[2]. The structure of the statically distorted $TeBr_6^{2\ominus}$ ion verifies these theoretical considerations. IR spectroscopic investigations of the solvate molecules of the calcium and the sodium compound give no indication of anion-oriented hydrogen bonding; consequently, the stronger polarizing effect of the bivalent cation in an anisotropic crystal field is

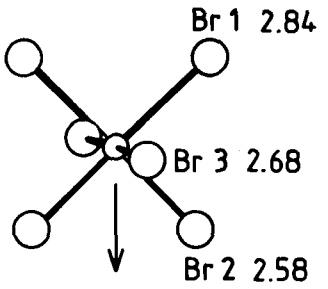

Fig. 2. Structure of the $TeBr_6^{2\ominus}$ ion in the crystal of $Ca(H_2O,HF)_7TeBr_6$; distances of the Br atoms from Te [Å] ($\sigma < 0.01$); angles [°] ($\sigma < 0.3$): Br1–Te–Br1 94.6, Br2–Te–Br2 91.0, Br3–Te–Br3 177.6, Br1–Te–Br2 87.2, Br1–Te–Br3 90.8, Br2–Te–Br3 89.1.

to be regarded as the primary cause for the stable static distortion.

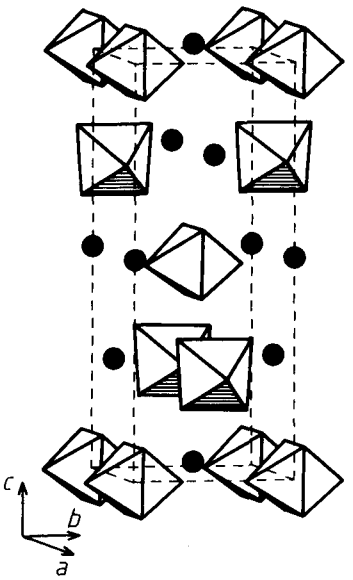

Fig. 3. Packing of the $Ca^{2\oplus}$ ions (spheres) and the distorted $TeBr_6^{2\ominus}$ octahedra in the unit cell of $Ca(H_2O,HF)_7TeBr_6$.

Apparently, these two conditions must be fulfilled for the stabilizing of the static distortion. For example, in the case of $Mg(H_2O)_6TeBr_6$—a compound whose crystal structure can be characterized with an arrangement of the cations and anions corresponding to that in the NaCl type structure (space group Pa3)—the regular (O_h) octahedronal array is found for the $TeBr_6^{2\ominus}$ group[14].

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[11] $Ca(H_2O,HF)_7TeBr_6$: Equimolar solution of $TeBr_4$ and CaF_2 in concentrated HF, excess HF/H_2O fumed off. The title compound crystallized as major product in the form of bright-red hygroscopic laths. With $TeBr_4$ in concentrated HF, the stable $TeBr_6^{2\ominus}$ ion is formed. $Ca(H_2O)_7TeBr_6$: Equimolar solution of TeO_2 and $CaCO_3$ in concentrated HBr. After evaporation to dryness/removal of excess $HBr(H_2O)$, growth of bright-red, hygroscopic crystals. The crystals of the two phases are isomorphic.

The content of solvate molecules was determined by thermogravimetric methods.

[12] $Ca(H_2O,HF)_7TeBr_6$: Nonius CAD4 diffractometer 293 K $Mo_{K\alpha}$ radiation, $I4_1md$, $a=8.985(9)$, $c=22.85(1)$ Å, $V=1844.69$ Å^3, $Z=4$, $R_w=0.089$ (the atoms of the solvate sheath of $Ca^{2\oplus}$ ignored). 500 independent reflections with $I>3\sigma(I)$, anisotropic temperature factors. The dynamics of the ions/molecules in the crystal precluded a satisfactory determination of the location of the solvate sheath at room temperature. $Ca(H_2O)_7TeBr_6$: 293 K: tetragonal, $a=8.905(3)$, $c=22.85(2)$ Å, $V=1812.13$ Å^3 (from single crystal measurements); 200 K: $a=8.984(2)$, $c=22.64(1)$ Å, $V=1826.99$ Å^3, unaltered crystal symmetry, volume dilation. Further details of the crystal structure investigation, are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD 51045, the names of the authors, and the journal citation.

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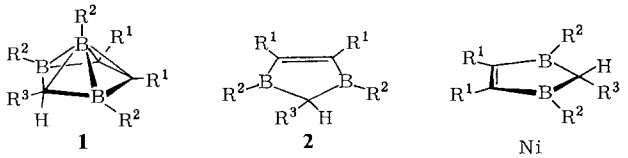
Carbaboranylnickel Complexes with the Novel η^5-2,3,5-Tricarbahexaboranyl Ligand**

By *Thomas Kuhlmann, Hans Pritzkow, Ulrich Zenneck,* and *Walter Siebert**

In Memoriam Earl M. Muetterties

Polyhedral *nido*-dicarbaborates $C_2B_{n-2}H_n^{2\ominus}$ undergo reactions at the pentagonal opening with metal ions and metal complex fragments to yield *closo*-carbametallaboranes[1]. In the case of the *nido*-tricarbahexaborate ion $C_3B_3H_6^{\ominus}$, alkyl derivatives of the 2,3,4-isomer[2] and of the tricarbonylmanganese complex $(\eta^5\text{-}C_3B_3H_4R_2)Mn(CO)_3$ (R = H, Me) have already been described. Attempts to prepare the 2,3,5-tricarbahexaborane **1** from the 2,3-dihydro-1*H*-1,3-diborole **2** and potential boranediyl generators have hitherto failed[3].

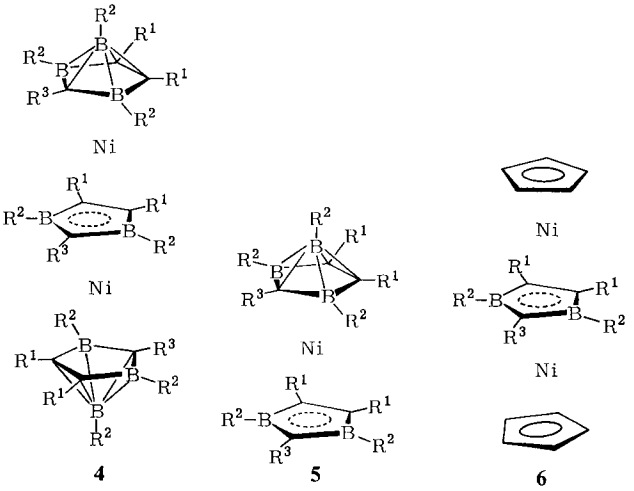


1 **2** Ni **3**

	R^1	R^2	R^3
a	Et	Et	Me
b	Et	Me	H
c	Me	Me	H

Scheme 1

We report here on the unexpected formation of the (η^5-2,3,5-tricarbahexaboranyl)nickel complexes **4**, **5**, and $Ni(\mathbf{5})_2$ by reacting bis(allyl)nickel with **2** in the molar ratio 1:2. The green, paramagnetic bis(carbaboranyl) triple-decker sandwich **4b** was obtained for the first time in trace amounts during the synthesis of bis[(η^3-allyl(μ,η^5-2,3-dihydro-1*H*-1,3-diborolyl)nickel]nickel complexes[4]. **4b**[5] and small amounts of **5b**[5] and $Ni(\mathbf{5b})_2$ are formed from the primary product **3b** by a methylboranediyl-transfer and stacking; a reaction whose mechanism still has to be clarified. Proof of the formation of the carbaborane from **3** was provided by the reaction of $Ni(\eta^3\text{-}C_3H_5)_2$ with **2c** under mild conditions. The golden-yellow sandwich complex **3c**[6] is slowly converted at 20 °C into **4c**, the turquoise-colored tetradecker sandwich complex $Ni(\mathbf{5c})_2$ and dark-colored oligomers[7]. In contrast, the formation of a (tricarbahexaboranyl)nickel complex is not observed with the sterically well shielded **3a**[8].



4 **5** **6**

Scheme 2. **a**, **b**, **c**: see Scheme 1.

Mass spectroscopic investigations of **4b** and the NMR data of the diamagnetic anion $\mathbf{4b}^{\ominus}$[5] indicate a triple-decker sandwich arrangement, which has been confirmed by an X-ray structure analysis[9]. Adjacent ligands in the molecule (Fig. 1) adopt an almost *trans*-conformation. The planes through the central ring and the base of the carbaboranyl ligands (deviations ≤ 0.04 Å) are parallel. The nickel atoms are closer to the carbaboranyl ring than to the μ-ligand (1.69, 1.70 and 1.73, 1.74 Å, respectively). The

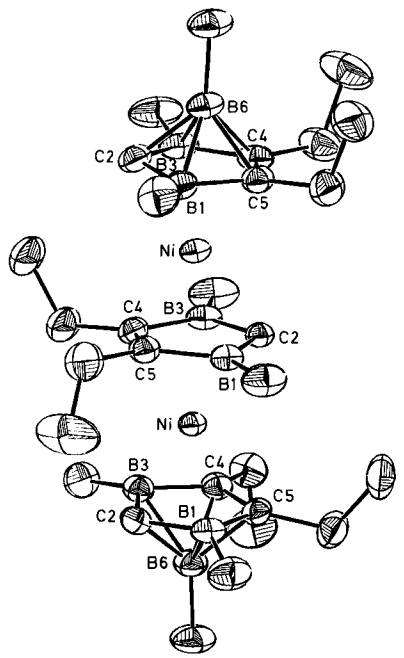


Fig. 1. Structure of **4b** in the crystal. Important bond lengths Å (standard deviations ±0.005 Å). Carbaboranyl ligand: B1(3)–C2 1.549–1.559, B1(3)–C4(5) 1.558–1.566, C4–C5 1.484, 1.485, B6–B1(3) 1.810–1.822, B6–C2 1.661, 1.674, B6–C4(5) 1.694–1.730; μ-ligand: B1(3)–C2 1.534, 1.542, B1(3)–C4(5) 1.586, 1.577, C4–C5 1.436.

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bond lengths and angles in the carbaboranyl sandwich **5b** are similar to those in **4b**[10]. Since the isolobal $C_3B_3H_6^{\ominus}$- and $C_5H_5^{\ominus}$-ligands each contribute five electrons to the complex formation, the 2,3,5-tricarbahexaboranyl compounds **4**, **5**, and Ni(**5**)$_2$ are the electronic analogues of the corresponding η^5-cyclopentadienyl(2,3-dihydro-1*H*-1,3-diborolyl)nickel complexes. Thus, like the paramagnetic triple-decker sandwich **6**[11], **4** has 33 valence electrons.

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[5] **4b/5b**: A solution of $(\eta^3\text{-}C_3H_5)_2Ni$ (2.8 mmol) and **2b** (5.4 mmol) in toluene (10 mL) was heated under reflux for 20 min. After removal of the solvent, **5b** was sublimed off at 65 °C/10^{-2} torr (0.05 mmol, 2%, m.p. 47 °C) and **4b** at 130 °C/10^{-2} torr (0.2 mmol, 15%, m.p. 81 °C); MS: *m/z* 609 ($M^{\oplus}$, 100%). **4b**$^{\ominus}$ (obtained from **4b** and potassium): ^{1}H-NMR ([D$_8$]THF): $\delta = -0.85$ (s, 6H, B–CH$_3$, apex), 0.44 (s, 12H), 0.55 (s, 1H), 0.63 (s, 6H), 1.03 (t, 12H), 1.18 (t, 6H), 1.61 (q, 4H), 1.8–1.9 (m, 8H), 2.23 (s, 2H). ^{11}B-NMR ([D$_8$]THF): $\delta = 10$ (br., 6B)–24.7 (s, 2B, apex). **5b**: ^{1}H-NMR (C_6D_6): $\delta = -0.51$ (s, 3H), 0.53 (s, 6H), 0.74 (s, 6H), 0.87 (t, 6H), 1.07 (t, 6H), 1.8–2.3 (m, 8H), 3.95 (s, 1H), 4.20 (s, 1H). MS: *m/z* = 378 ($M^{\oplus}$, 100%). ^{11}B-NMR (C_6D_6): $\delta = -3.9$ (s, 1B, apex), 13.4 (s, 2B), 37 (br., 2B, η^5-C_3B_2). Analogously to **3c**, **3b** is converted into **5b** and Ni(**5b**)$_2$ at 20 °C [8].
[6] **3c**: A solution of Ni(η^3-C_3H_5)$_2$ (4.5 mmol) and **2c** [12] (9.2 mmol) in petroleum ether (20 mL) was stirred for 30 min at 20 °C. After removal of the solvent, sublimation at 50 °C/10^{-3} torr furnished **3c** (2.8 mmol, 62%; m.p. > 60 °C (rapid conversion). ^{1}H-NMR (C_6D_6): $\delta = -2.32$ (d, 2H), 0.13 (d, 2H), 0.39 (s, 6H), 0.70 (s, 6H), 1.48 (s, 6H), 1.59 (s, 6H). ^{11}B-NMR (C_6D_6): $\delta = 45.1$ (s, 2B), 39.4 (s, 2B). MS: *m/z* = 298 ($M^{\oplus}$, 77%).
[7] Ni(**5c**)$_2$: Recrystallization of **3c** in CH_2Cl_2 afforded a deep-green solution, from which Ni(**5c**)$_2$ was isolated by sublimation at 155 °C/10^{-3} torr. ^{1}H-NMR (C_6D_6): $\delta = -0.84$ (s, 6H), 0.63 (s, 12H), 0.69 (s, 12H), 1.41 (s, 12H), 1.43 (s, 12H), 3.04 (s, 2H), 3.08 (s, 2H). MS: *m/z* = 702 (46%). According to the EI, FD and FAB mass spectra the residue remaining after sublimation contained oligomers with mass differences of 177 ($\triangleq {}^{58}Ni(C_3{}^{11}B_2Me_4H)$, stacking unit of the oligomers) and the expected isotopic pattern.
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[9] **4b**: P2$_1$/a, $a = 24.821(7)$, $b = 15.043(5)$, $c = 9.256(4)$ Å, $\beta = 94.36(2)°$, $V = 3446.1$ Å^3, $Z = 4$; $R = 0.037$ for 6933 observed reflections (Stoe two-circle diffractometer, $Mo_{K\alpha}$). Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD 50994, the names of the authors, and the journal citation.
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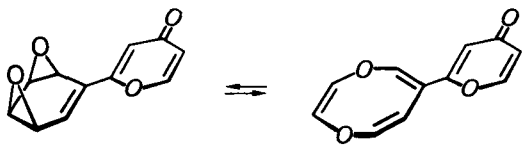
Synthesis of the Antibiotic LL-Z1120—Contribution to an Understanding of the 1,4-Dioxocine System

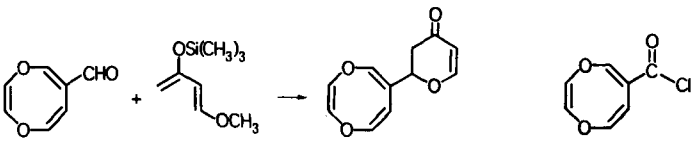
By *Hans-Josef Altenbach*, Johann Lex, Dieter Linkenheil, Burkhard Voss,* and *Emanuel Vogel**

Following their synthesis some 20 years ago[1], arene monoxides were soon recognized as primary intermediates of the oxidative metabolism of aromatic compounds[2]. This finding gave ample justification for assuming that representatives of the subsequently synthesized benzene di-[3] and trioxides[4] also occur in nature. Indeed, in 1972 *Borders* and *Lancaster* were able to isolate from an unspecified type of fungus the antibiotic **1** known as LL-Z1220[5], a benzene dioxide with a γ-pyrone substituent. Evidence for the existence of a *syn*-benzene dioxide derivative was provided by an NMR comparison with the *syn*- and *anti*-benzene dioxide parent compounds[3] and by the fact that **1** thermally equilibrates with the 1,4-dioxocine valence tautomer **2**, which is likewise antibiotically active[5c]. We report here on the first synthesis of **1**.



1, LL-Z1220 **2**

In view of the chemical sensitivity of *syn*-benzene dioxides it seemed appropriate to construct the target molecule in the following stages: 1) Preparation of 1,4-dioxocine-6-carbaldehyde **3**[6] as the key compound of the synthesis; 2) conversion of **3** into **2** using the aldehyde function for the building up of the γ-pyrone substituent; and 3) thermal equilibration of **2** with **1** and separation of **1** from the equilibrium mixture frozen at room temperature. In the light of previous studies[5c, 6] the actual synthetic problem is reduced to the conversion of the aldehyde **3** into the valence tautomer **2** of the natural product. This step should be realizable[9] by reaction of **3** with the Danishefsky diene **4**[7] or with lithiated 4-methoxy-3-buten-2-one **7**, and subsequent dehydrogenation of the expected product, dihydro-γ-pyrone **5**, according to one of the methods[8] that have already proven useful in flavone and chromone chemistry.



3 **4** **5** **6**

Scheme 1. **3**→**5**: 1) THF, −40 °C, 1 equiv. BF_3–OEt_2, 4 h; 0 °C, H_2O, $NaHCO_3$ solution.

3 was allowed to react with **4** (1 equivalent of each) in tetrahydrofuran (THF) in the presence of boron trifluoride-etherate at −40 °C; after neutralization with sodium bicarbonate solution and work-up by chromatography on silica gel (ether) the expected **5** was obtained [colorless needles, m.p. 61–62 °C (ether/pentane, 1:1); yield 25%][12], together with the very labile **8** (ca. 10%)[12] and unchanged **3**. The compound **8**, apparently the product of a Mukaiyama aldol addition[13], readily cyclizes to **5** on subsequent treatment with trifluoroacetic acid, from which it can be concluded that **5** is formed, at least in part, via **8**. For the generation of **5** it is, however, more advantageous to react **3** with the enolate **7** prepared from 4-methoxy-3-buten-2-one and lithium bis(trimethylsilyl)amide and to cyclize compound **8** thus formed to **5** with trifluoroacetic

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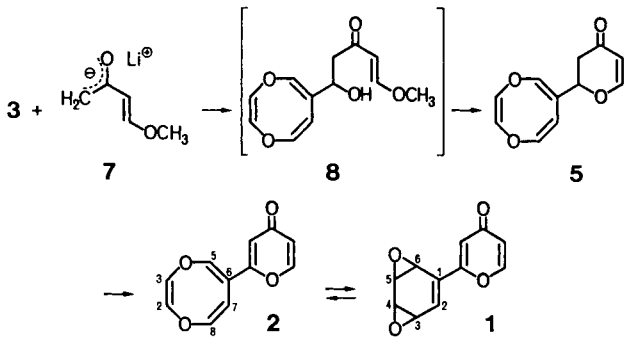
acid in benzene (yield 60%). Attempts to dehydrogenate **5** to **2** conventionally, invariably led to undefined product mixtures, even on using relatively mild conditions[8]. It was therefore surprising that the reaction of **5** with iodine/dimethyl sulfoxide/conc. sulfuric acid[14] at 90°C gave the desired compound **2**. After separation by preparative thin-layer chromatography (silica gel, ethyl acetate), the compound **2** crystallized from ether in the form of colorless needles [m.p. 85—87°C (lit. [5c]: 84—87°C), yield 5%]. The identity of the compound with the 1,4-dioxocine valence tautomer of LL-Z1220 was verified by a comparison of the spectra[5c, 12].



Scheme 2. **7**: THF, −78°C, $LiN[Si(CH_3)_3]_2$, 10 min; **3**→**8**: solution of **3** in THF added dropwise to **7** at −78°C, 15 min, 0°C, H_2O; **8**→**5**: benzene/trifluoroacetic acid, RT, 18 h; **5**→**2**: DMSO/I_2/conc. H_2SO_4, 90°C, 20 min; **2**⇄**1**: acetone, 5 h, reflux.

The thermal isomerization of **2** to **1** was carried out in acetone (5 h, reflux), since a ^{1}H-NMR study of the solvent-dependence of the equilibrium **1**⇄**2** had revealed that the concentration of **1** in this solvent is relatively high (ca. 30%). The large difference in polarity of **1** and **2** allowed the ready separation of the two valence tautomers by chromatography on silica gel (ethyl acetate). Racemic **1**, recrystallized from ethyl acetate [colorless needles, m.p. 159—160°C (decomp.)], shows the same spectra as optically active LL-Z1220 [m.p. 148°C (decomp.)][5a, 12].

In view of the current interest in 1,4-diheterocines (potential 10π arenes)[15]—especially regarding the influence of the heteroatoms on the properties of these compounds—knowledge of the molecular structure of the 1,4-dioxocine **2** was desirable. According to the ^{1}H-NMR spectrum, 1,4-dioxocine itself contains localized π bonds and should therefore have a twist-boat-chair or half-chair conformation. The reason why 1,4-dioxocine—in contrast to the 1,4-dihydro-1,4-diazocine[15b] and 4*H*-1,4-oxazocine[15c]—does not qualify as a 10π arene is because of the lower tendency of the oxygen atoms to undergo π-electron delocalization. The X-ray structure analysis of **2** confirms the presumed non-planar conformation of the 1,4-dioxocine moiety (Fig. 1, left). The eight-membered ring has a twist-boat-chair conformation with the 5,6-double bond and the γ-pyrone ring being almost coplanar[16].

Since the ^{1}H-NMR signals of H-2, 3, 7, and 8 of 1,4-dioxocine-6-carbaldehyde **3** and 1,4-dioxocine-6-carboxylic acid chloride **6**[6] show a—possibly geometry-related—slight downfield shift compared to the corresponding signals of **2**, we also subjected crystalline **6** to a structure analysis. The eight-membered ring in **6**, with a coplanar arrangement of the substituent, is practically planar (Fig. 1, right)[16]. If it is assumed that unsubstituted 1,4-dioxocine

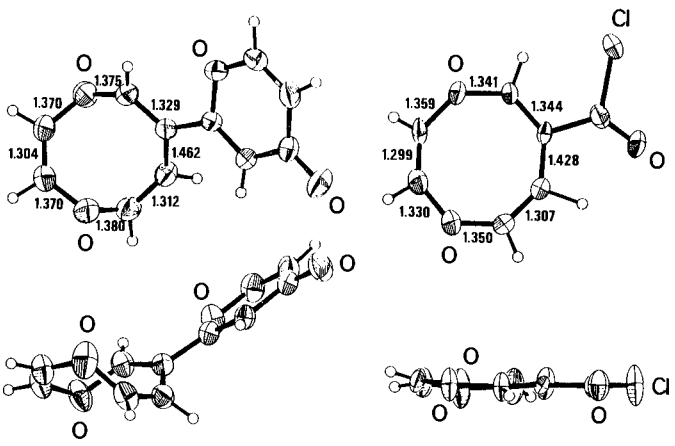


Fig. 1. Molecular structure of **2** (left) and **6** (right) in the crystal [16]. Top-view (top) and sideview (bottom). Selected bond lengths [Å].

is nonplanar, then the conjugative effect of the acceptor substituent COCl must be decisive for the planarization of the eight-membered ring in **6**. In the case of **2**, with the γ-pyrone ring as acceptor, this effect does not operate, because the substituent in a planarized 1,4-dioxocine ring is hindered by H—H interactions from assuming a coplanar arrangement.

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[9] The elegant methods of *M. Koreeda* et al. [10] and of *B. Ganem* et al. [11] for converting carboxylic acid chlorides with **7** directly into α-substituted γ-pyrones, developed with a view to synthesizing natural products containing a γ-pyrone structure unit, gave products no longer containing the 1,4-dioxocine skeleton in exploratory investigations using **6**. Apparently, the 1,3-diketone formed as intermediate does not cyclize in the desired way to give **2** but attacks the activated enol-ether double bond of the 1,4-dioxocine, with opening of the eight-membered ring.

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[12] **1**: ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 3.64$ (m, 2H), 3.87 (m, 2H), 7.16 (m, H-2), 6.34 (m, H-11), 6.62 (d, H-9, $J_{9,11} = 2.4$ Hz), 7.75 (d, H-12,

$J_{11,12}$ = 6.0 Hz).—**2**: ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 5.45, 6.52 (AX system, H-7,8, $J_{7,8}$ = 6.8 Hz), 5.88, 5.98 (AB system, H-2,3, $J_{2,3}$ = 4.1 Hz), 6.28 (m, H-11,13), 7.21 (s, H-5), 7.67 (d, H-14, $J_{13,14}$ = 6.1 Hz).—**5**: ^{1}H-NMR (90 MHz, $CDCl_3$): δ = 2.30—3.05 (m, H-11,11'), 4.90 (m, H-10), 5.35, 6.60 (AX system, H-7,8, $J_{7,8}$ = 7.2 Hz), 5.50, 7.50 (AX system, H-13,14, $J_{13,14}$ = 6.0 Hz), 5.90, 6.05 (AB system, H-2,3, $J_{2,3}$ = 4.5 Hz), 6.80 (s, H-5).—**8** (contaminated with **5**): ^{1}H-NMR (90 MHz, $CDCl_3$): δ = 2.65 (m, H-11,11'), 3.50 (br. s, OH), 3.70 (s, OCH_3), 4.60 (m, H-10), 5.30, 6.40 (AX system, H-7,8, $J_{7,8}$ = 7.5 Hz), 5.55, 7.60 (AX system, H-13,14, $J_{13,14}$ = 12.0 Hz), 5.75, 5.95 (AB system, H-2,3, $J_{2,3}$ = 4.4 Hz), 6.60 (s, H-5).

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[16] Crystal data: **2**: monoclinic, space group $P2_1/c$, a = 7.905(1) Å, β = 109.60(1)°, Z = 4; 1462 reflections, R = 0.050.—**6**: monoclinic, space group $P2_1/c$, a = 3.808(4), b = 12.487(8), c = 15.150(13) Å, β = 92.33(9)°, Z = 4; 951 reflections, R = 0.099.—Further details of the crystal structure investigations are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD 51057, the names of the authors, and the journal citation.

$Cp_2Mo_2(CO)_4P_2$ as Complex Ligand**

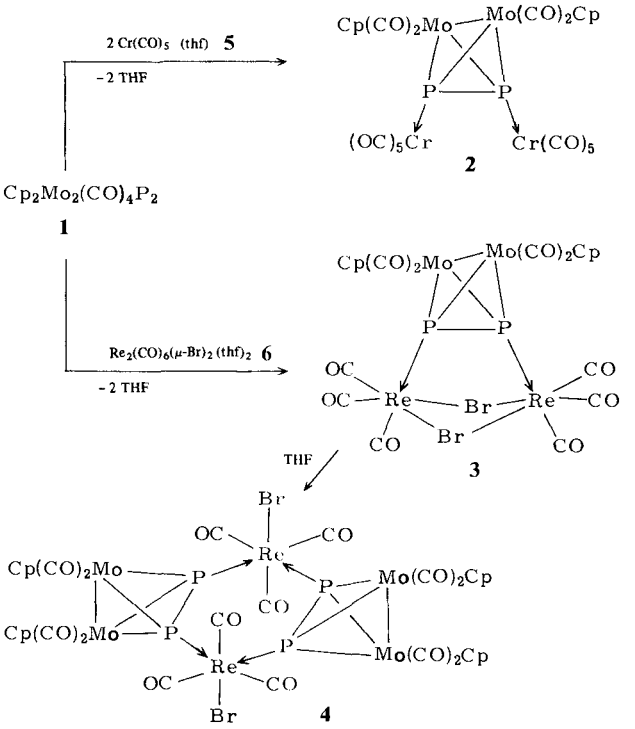
By *Otto J. Scherer**, *Helmut Sitzmann*, and *Gotthelf Wolmershäuser*

Dedicated to Professor Kurt Issleib on the occasion of his 65th birthday

All attempts to coordinate the lone electron pairs of the P_2 unit of the isolated complex $Co_2(CO)_6P_2$ with transition metals were unsuccessful[1a] and led to the assumption that this molecular moiety has only very weak donor properties[1a,b]. If, however, halogenophosphanediyl or halogenophosphane complexes are allowed to react with tetracarbonylcobaltate, then, e.g., $Co_2(CO)_6P_2[Cr(CO)_5]_2$ can be synthesized, a complex in which for the first time P_2 functions as an eight-electron ligand[2].

The complex $Cp_2Mo_2(CO)_4P_2$ **1**[3] prepared by us is suitable for both terminal as well as for bridging P-coordination. Thus, **1** reacts with the chromium complex **5** to give **2**, and with the rhenium complex **6** to give **3**; in tetrahydrofuran, **3** is transformed into **4**. Complexes **2** (readily soluble in CH_2Cl_2) and **4** (soluble in CH_2Cl_2 in traces) form dark red crystals[4], while **3** (sparingly soluble in CH_2Cl_2) forms orange-red crystals[4].

The crystal structure analysis[5] shows that in the case of **3** (Fig. 1) a Re_2Br_2 four-membered ring (angle between the normals to the $ReBr_2$ planes 37.9°) is bridged by the P_2 edge of the P_2Mo_2 cluster. In the case of the centrosymmetric molecule **4** (Fig. 2), the two Re atoms (undistorted octahedral environment) and the P_2 units form a planar six-membered ring (sum of angles 719.6°). The bond lengths and angles of the coordinated P_2Mo_2 tetrahedron



in **3** and **4** differ very little from those of the free ligand **1**[3a]. The Re–P bond lengths lie within the range of bond lengths found in $[Re_2(\mu\text{-}Br)_2(CO)_6(\mu\text{-}Ph_2P\text{–}PPh_2)]$[6a], $[Re_2(\mu\text{-}Br)_2(CO)_6(\mu\text{-}RR'N\text{–}P{=}NR)]$[6b], and $[Re_2(\mu\text{-}Br)_2(CO)_6(\mu\text{-}H_3CPNR)_2]$[6c], R = CMe_3, R' = $SiMe_3$.

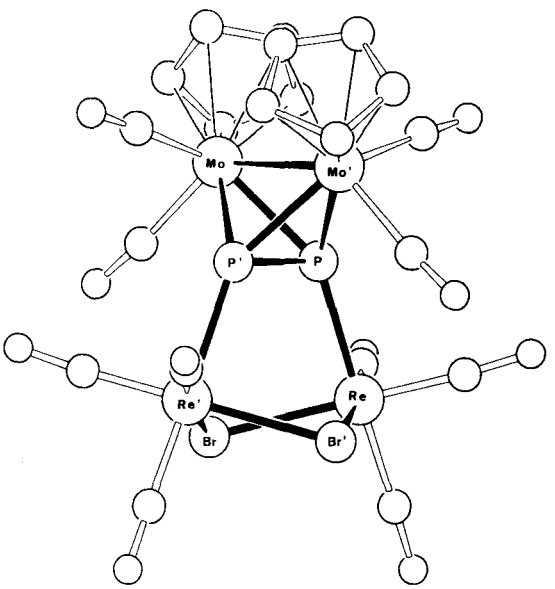


Fig. 1. Structure of **3** in the crystal. Selected bond lengths [Å] and angles [°]: P–P' 2.093(8), Mo–Mo' 3.077(2), Re···Re' 3.878(1), P–Mo 2.507(4), P'–Mo 2.427(4), Re–P 2.490(4), Re–Br 2.662(2), Re'–Br 2.661(2); P'–P–Re 110.7(6), Re–Br–Re' 93.5(1), Br–Re–Br' 79.2(1), P–Re–C(tr) 179.7(3); the molecule has crystallographic C_2 symmetry.

The synthesis of **2**, **3**, and **4** demonstrates the universal ligand properties of **1** and extends the hitherto only known type of complex with P_2 as eight-electron ligand[2] by the first examples with bridging coordination.

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[**] This work was supported by the Fonds der Chemischen Industrie (Doctorate Grant for *H. S.*).

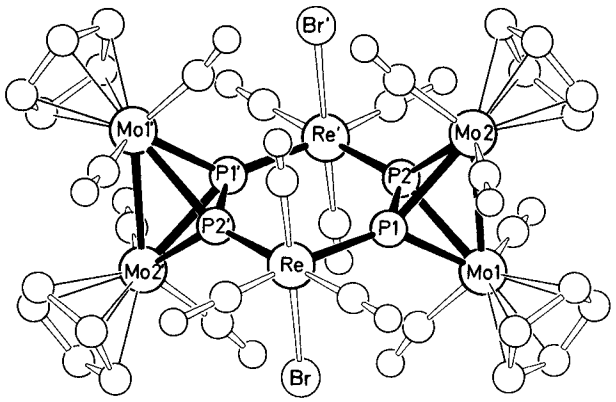

Fig. 2. Structure of 4 in the crystal. Selected bond lengths [Å] and angles [°]: P1–P2 2.071(9), P1–Re 2.477(7), P2'–Re 2.489(7), Re–Br 2.596(3), Mo1–Mo2 3.034(2), P1–Mo1 2.441(7), P1–Mo2 2.542(7), P2–Mo1 2.536(6), P2–Mo2 2.429(6), P2–P1–Re 135.4(3); Re'–P2–P1 135.3(3), P1–Re–P2' 89.1(3), Mo1–P1–Re 141.6(3), Mo2–P1–Re 139.3(3), Mo1–P2–Re' 140.2(3), Mo2–P2–Re' 140.2(3).

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[4] Experimental: **2**: A solution of **1** (118 mg, 0.239 mmol) in THF (10 mL) was treated at room temperature with a solution of **5** [prepared from 117 mg (0.532 mmol) $Cr(CO)_6$ in 70 mL THF by irradiation, 150 W mercury high-pressure lamp, 12 °C] and the mixture stirred for 12 h. After addition of ca. 10 mL Florisil the mixture was evaporated down and chromatographed on Florisil with toluene/pentane (2:1) (Column: diameter 2 cm, length ca. 5 cm). On evaporating to dryness, the red eluate afforded 95 mg (45%) ruby-red crystals. IR (C_6H_6): ν(CO) = 2070 (s), 2058 (s), 2002 (vs), 1985 (s), 1890 (br., vs) cm^{-1}; ^{1}H-NMR (90 MHz, CD_2Cl_2, TMS int.): δ = 5.23 (s, C_5H_5); ^{31}P{^{1}H}-NMR (213 K, THF, 85proz. H_3PO_4 ext.): δ = −36.7 (s); ^{13}C{^{1}H}-NMR (233 K, CH_2Cl_2, TMS int.): δ = 221.4 (s, 2C, MoCO), 217.6 (s, 1C, CrCO), 216.0 (s, 4C, CrCO).—**3**: IR (KBr): ν(CO) = 2045 (s), 2015 (br., vs), 1968 (br., vs), 1925 (br., vs), 1892 (br., vs) cm^{-1}; ^{1}H-NMR (200 MHz, CD_2Cl_2, TMS int.): δ = 5.63 (t, ^3J(PH) = 1.1 Hz); ^{31}P{^{1}H}-NMR (298 K, CH_2Cl_2, 85proz. H_3PO_4 ext.): δ = −78.5 (s).—**4**: IR (KBr): ν(2024 (vs), 2018 (vs), 1960 (br., vs), 1940 (br., vs) cm^{-1}.—**3**: A solution of **1** (69.7 mg, 0.140 mmol) in dichloromethane (3 mL) was added dropwise to a stirred solution of **6** (118.0 mg, 0.140 mmol) in dichloromethane (4 mL) at room temperature. After ca. 10 s, a tile-red, microcrystalline powder separated out. After 10 minutes' stirring, the mixture was concentrated to ca. 3 mL and the supernatant liquor pipetted off. The precipitate was washed three times with ca. 1 mL pentane and dried in a vacuum (oil-pump). Yield 153 mg (91%). A solution of **1** (39.4 mg, 0.079 mmol) in dichloromethane (1.5 mL) was added dropwise at −78 °C to a stirred solution of **6** (67.1 mg, 0.079 mL) in dichloromethane (6 mL) and the resulting clear solution was allowed to stand for 4—5 d at −15 °C. Orange crystals are formed in ca. 80% yield.—**4**: 20 mg (0.0167 mmol) **3** was dissolved in 5 mL THF and the resulting solution immediately cooled to −80 °C. On thawing out at room temperature, red crystals separated from the solution. The solution was pipetted off and the crystals washed three times with ca. 1 mL pentane and dried in a vacuum (oil-pump). Yield 5 mg (34%).

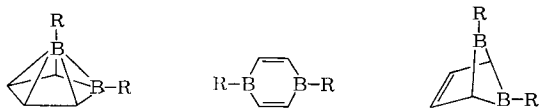
[5] **3**: C2/c, a = 17.411(4), b = 10.635(4), c = 17.161(3) Å, β = 117.96(2)°, Z = 4, ρ_{calc} = 2.83 g cm^{-3}. 2194 independent reflections ($Mo_{K\alpha}$, $2\theta \leq 50°$), 1854 observed ($F_0^2 \geq 2.0\sigma(F_0^2)$), 172 parameters; R = 0.058, R_w = 0.0555. **4**: P$\bar{1}$, a = 12.421(5), b = 10.430(2), c = 11.380(2) Å, α = 107.09(1), β = 102.80(2), γ = 97.46(2)°; Z = 1, ρ_{calc} = 2.16 g cm^{-1}, 4294 independent reflections ($Mo_{K\alpha}$, $4° \leq 2\theta \leq 50°$), 3267 observed ($F_0^2 \geq 2.0\sigma(F_0^2)$), R = 0.0855, R_w = 0.0859. In the data collection, a drop in the intensity of the control reflections of 13.3% was observed; this was taken into account in the data reduction. The parameters of the disordered thf-molecule (ca. 1 mol per formula unit) and the parameters of the hydrogen atoms were not included in the refinement. Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2 on quoting the depository number CSD 51 002, the names of the authors, and the journal citation.

[6] a) J. L. Atwood, J. K. Newell, W. E. Hunter, I. Bernal, F. Calderazzo, I. P. Marani, D. Vitali, *J. Chem. Soc. Dalton Trans. 1978*, 1189; b) O. J. Scherer, J. Kerth, R. Anselmann, W. S. Sheldrick, *Angew. Chem. 95* (1983) 1003; *Angew. Chem. Int. Ed. Engl. 22* (1983) 984; c) O. J. Scherer, R. Anselmann, W. S. Sheldrick, *J. Organomet. Chem. 263* (1984) C26.

$C_4B_2H_6$ Isomers: Destabilization of the *nido*-Carbaborane Structure by Amino Substituents and a Novel Classical Isomer

By *Gerhard E. Herberich**, *Holger Ohst*, and *Horst Mayer*

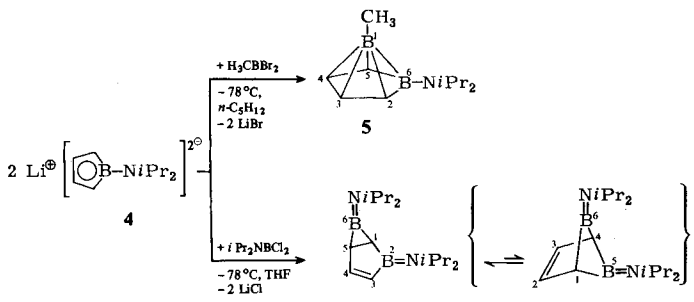
Previously known $C_4B_2H_6$ derivatives exist in either the *nido*-carbaborane **1**[1] or 1,4-dibora-2,5-cyclohexadiene **2**[2] structural form. According to quantum chemical calculations the substituent at the boron atom governs the thermodynamic stability of the isomers. For R = H the carbaborane structure **1** is more stable, and for R = F the 1,4-dibora-2,5-cyclohexadiene structure **2**; in both cases the hypothecital isomer **3** is least favourable energetically[3]. π-Interactions between R and the boron atom reduce the electron deficiency in **2** and **3** and, hence, stabilize the classical structures.



1 **2** **3**

We report here the first amino derivatives of the $C_4B_2H_6$ family. These can be synthesized in a designed way from the borole dianion **4**[4]. Thus, we obtained **5** (Scheme 1), the first carbaborane amino-substituted at a boron atom[5], and **6**, the first 2,6-diborabicyclo[3.1.0]hex-3-ene derivative[6]. With *one* amino substituent the carbaborane structure is labilized and, in contrast to the parent compound **1** (R = H), **5** is surprisingly sensitive towards air and protic reagents. With *two* amino substituents the novel classical structure **6** is now stable.

Variable temperature ^{1}H-NMR spectroscopic studies indicate that **6** undergoes a tautomeric skeletal rearrangement with $\Delta G^+ = 45 \pm 3$ kJ mol^{-1}[7]. At room temperature **6** has effectively C_{2v} symmetry and the iPr$_2$N groups rotate rapidly about the B–N bond; all eight CH_3 groups are equivalent and the signals of all four ring C atoms in the ^{13}C-NMR spectrum are broadened by ^{11}B(^{10}B) quadrupo-



Scheme 1.

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lar interaction. Presumably **6** therefore exists in equilibrium with the less stable isomer **7** involving $[1,3]_s$-sigmatropic shifts; an alternative mechanism via a *nido*-carbaborane structure **1** ($R=iPr_2N$) is improbable, since the known derivatives of **1** have static structures with nonequivalent RB groups[1]. No evidence was found for the occurrence of **2** ($R=iPr_2N$).

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CAS Registry numbers:
4, 89119-17-5; **5**, 93110-37-3; **6**, 93110-38-4; **7**, 93110-39-5; CH_3BBr_2, 17933-16-3; i-Pr_2NBCl_2, 44873-49-6.

[1] Parent compound: E. Groszek, J. B. Leach, G. T. F. Wong, C. Ungermann, T. Onak, *Inorg. Chem. 10* (1971) 2770; V. R. Miller, R. N. Grimes, *ibid. 11* (1972) 862; alkyl derivates: P. Binger, *Tetrahedron Lett. 1966*, 2675; P. Binger, *Angew. Chem. 80* (1968) 288; *Angew. Chem. Int. Ed. Engl. 7* (1968) 286; L. Killian, B. Wrackmeyer, *J. Organomet. Chem. 132* (1977) 213; H.-O. Berger, H. Nöth, B. Wrackmeyer, *Chem. Ber. 112* (1979) 2884; B. Wrackmeyer, *Z. Naturforsch. B37* (1982) 412.

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[3] R. N. Camp, D. S. Marynick, G. D. Graham, W. N. Lipscomb, *J. Am. Chem. Soc. 100* (1978) 6781.

[4] G. E. Herberich, H. Ohst, *Z. Naturforsch. B38* (1983) 1388.

[5] **5**: Colorless, sensitive to air and water, isolated by fractional distillation, pure according to ^{1}H-NMR spectroscopy, yield 17%.—^{1}H-NMR (90 MHz, $CDCl_3$): $\delta=5.45$ ("t", $J=3.9$ Hz; 3-/4-H), 3.37 ("t", $J=3.9$ Hz; 2-/5-H), 3.50 (sept, $^3J=6.7$ Hz, $CH(CH_3)_2$, 2H), 1.16 (d, $^3J=6.7$ Hz, $CH(CH_3)_2$, 12H), −0.13 (br., BCH_3).—^{11}B-NMR ($CDCl_3$): $\delta=23$ (BN), −48 (BCH_3).—^{13}C-NMR ($CDCl_3$): $\delta=98$ (d, $^1J(CH)=180$ Hz, C-3/4), 65 (m, br., C-2/5), 47 (d, $^1J(CH)=132$ Hz, $CH(CH_3)_2$, 2C), 23 (q, $^1J(CH)=126$ Hz, $CH(CH_3)_2$, 4C), BCH_3 not observed.—MS (70 eV): m/z 189 ($M^{\oplus}$, 17%), 174 ($M^{\oplus}-CH_3$, 100).

[6] **6**: Colorless solid, sensitive to air and water, m.p. = 21 °C, isolated by fractional distillation, pure according to elemental analyses, yield 62%.—^{1}H-NMR (80 MHz, CD_2Cl_2, −70 °C): $\delta=7.19$ (d, $^3J=7.0$ Hz; 4-H), 5.69 (d, $^3J=7.0$ Hz; 3-H), 4.02 (m, $CH(CH_3)_2$, 1H), 3.25 (m, $CH(CH_3)_2$, 3H), 2.23 (d, $^3J=6.2$ Hz; 5-H), 1.12 (m, 1-H and $CH(CH_3)_2$, 24H).—^{11}B-NMR (32 MHz, CD_2Cl_2, −50 °C): $\delta=44$ (width at half-height 890 Hz at −50 and 140 Hz at 100 °C; resolution into two signals is hardly to be expected).—^{13}C-NMR (CD_2Cl_2, −70 °C): $\delta=160.8$ (d, $^1J(CH)=154$ Hz, C-4), 127.8 (d, br., $^1J(CH)=146$ Hz; C-3), 28.5 (br., C-5), 16.3 (d, br., $^1J(CH)=146$ Hz, C1), signals with centroids at 52.9, 52.1, 50.9, 43.6 ($CH(CH_3)_2$, 4C), signals with centroids at 25.4—21.6 ($CH(CH_3)_2$, 8C), of which 6 CH_3 groups can be distinguished.—MS (70 eV): m/z 274 ($M^{\oplus}$, 73%), 259 ($M^{\oplus}-CH_3$, 45), 231 ($M^{\oplus}-iPr$, 80), 174 ($M^{\oplus}-NiPr_2$, 100).—Room temperature NMR spectra with numbering as in **7**: ^{1}H-NMR (80 MHz, CD_2Cl_2, 25 °C): $\delta=4.71$ ("d"; 2-/3-H), 3.40 ("d"; 1-/4-H), 3.48 (sept., $^3J=6.7$ Hz, $CH(CH_3)_2$, 4H), 1.14 (d, $^3J=6.7$ Hz, $CH(CH_3)_2$, 24H).—^{11}B-NMR (32 MHz, CD_2Cl_2, 25 °C): $\delta=44$.—^{13}C-NMR (20 MHz, CD_2Cl_2, 25 °C): $\delta=95$ (br., C-2/3), 74 (br; C-1/4), 50 (d, $^1J(CH)=134$ Hz, $CH(CH_3)_2$, 4C), 24 (q, $^1J(CH)=126$ Hz, $CH(CH_3)_2$, 8C).

[7] Estimated from

$$\Delta G^{+}=1.914\times10^{-2}\,T_c(9.97+\lg|T_c/\Delta\nu|)\ \text{kJ mol}^{-1}\ \text{K}^{-1}$$

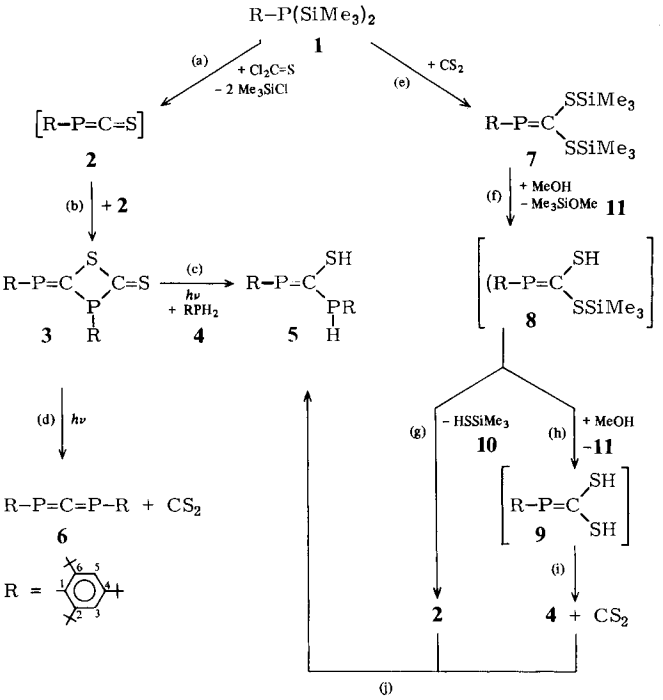
J. Sandström: *Dynamic NMR Spectroscopy*, Academic Press, New York 1982, p. 93ff.

First Evidence for the Existence of a Phosphathioketene**

By *Rolf Appel*, Peter Fölling, Lothar Krieger, Mustafa Siray,* and *Falk Knoch*

The number of compounds containing cumulated double bonds with participation of λ^3-phosphorus in groups such as −P=C=O[1], −P=C=N−[2], −P=C=C<[3], and −P=C=P−[3b,4] has increased tremendously in recent years. As a further extension in this series of compounds it has now been possible to demonstrate the presumed existence of a compound containing the −P=C=S− sequence.

In analogy to the synthesis of the first stable phosphaketene[1b], we allowed 2,4,6-tri-*tert*-butylphenylbis(trimethylsilyl)phosphane **1** to react with thiophosgene in dioxane. On addition of acetonitrile, red crystals precipitate, which according to elemental analysis, molar mass determination, NMR spectroscopic and mass spectroscopic investigations, and X-ray structure analysis constitute the dimer **3** of the phosphathioketene **2**[5] (Fig. 1) [reactions (a) and (b)]. The phosphathioketone **2** assumed to be formed as intermediate dimerizes, like ketenes[6], in an unsymmetrical [2+2]-cycloaddition.



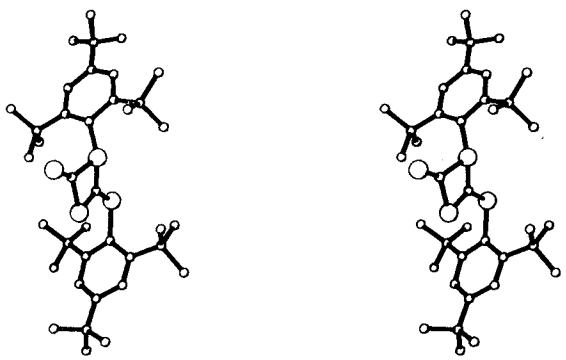


Fig. 1. Stereoscopic diagram of the structure of **3** in the crystal.

Phosphaketenes behave differently: the dimerization of *tert*-butylphosphaketene proceeds symmetrically at the PC double bond[1a], and in the case of the stable 2,4,6-tri-*tert*-

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[**] Lower Coordinated Phosphorus Compounds, Part 35.—Part 34: R. Appel, C. Casser, M. Immenkeppel, F. Knoch, *Angew. Chem. 96* (1984) 905; *Angew. Chem. Int. Ed. Engl. 23* (1984) 895.

butylphenylphosphaketene no dimerization has hitherto been observed, but, instead, a trimerization with elimination of a CO molecule to give a five-membered heterocycle[7].

An additional indication of the intermediate formation of the apparently very reactive **2** was afforded on irradiation of **3** in the presence of the phosphane **4** [reaction (c)]. It was found that the 1,3-diphosphapropene **5**[8] is formed, presumably by addition of **4** to the species **2** formed by cycloreversion of **3**. The structure of **5** is confirmed by X-ray structure analysis[8b] (Fig. 2); SH/PH tautomerization to give a symmetric diphosphathiourea can be ruled out, both in the crystal as well as in solution. Not only symmetric but also unsymmetric cleavage of the four-membered ring of **3** is observed. UV-Irradiation of **3** in the absence of the phosphane **4** leads to formation of carbon disulfide and the 1,3-diphosphaallene **6**[3a,4] [reaction (d)]. The cleavage of diketene into allene and CO_2 proceeds analogously[9].

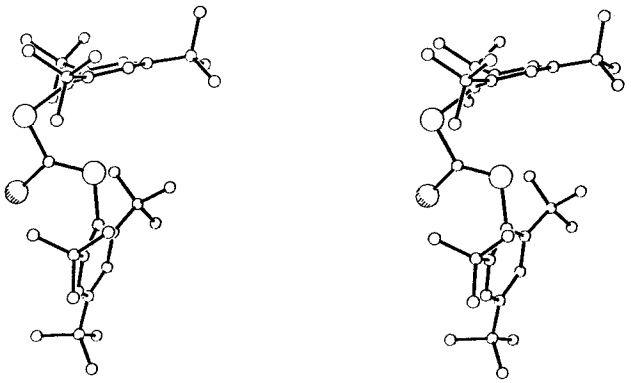

Fig. 2. Stereoscopic diagram of the structure of **5** in the crystal.

An independent synthesis of the readily isolable diphosphapropene **5** was accomplished by careful methanolysis of the [bis(silylthio)methylene]phosphane **7**[11], obtainable by reaction of **1** with carbon disulfide according to the method of *Becker* et al.[10] [reaction (e)]. We assume that cleavage of methoxytrimethylsilane **11** and silanethiol **10** likewise leads, via **8**, to intermediary formation of phosphathioketene **2** [reactions (f) and (g)]. In the reactions (h) and (i), methanolysis of **8** leads to the dithiol **9**, which decomposes into the phosphane **4** and carbon disulfide. **2** reacts with **4** to give the 1,3-diphosphapropene **5** [reaction (j)].

The phosphaallene **6** and methoxytrimethylsilane **11** were identified by comparison with authentic samples. The carbon disulfide formed according to route (i) and the hydrogen sulfide formed by hydrolysis of **10** could be detected by Dräger inspection tubes.

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[5] **3**: decomp. at 160°C, MS (70 eV): *m/z* 640 (0.4%, $M^{\oplus}$); molar mass, calculated: 640, found: 622 (vapor pressure).—$^{31}P\{^1H\}$-NMR (32.203 MHz, $CDCl_3$, standard 85proz. H_3PO_4): $\delta = +68.9$ (d, $^2J(PP) = 60.9$ Hz, C–*P*(Aryl)–C), +228.6 (d, $^2J(PP) = 60.9$ Hz, C=*P*(Aryl)). $^{13}C\{^1H\}$-NMR (22.628 MHz, $CDCl_3$): $\delta = 31.1$—38.9 (*t*Bu), 122.1—158.3 (aromat.), 171.7 (dd, $J(PC) = 24.1$, $J(PC) = 73.2$ Hz; P=*C*–P), 239.8 (dd, $J(PC) = 31.5$, $^3J(PC) = 18.3$ Hz; C=S). X-ray structure analysis of **3**: P$\bar{1}$, $a = 1061.3(3)$, $b = 1105.3(3)$, $c = 1733.8(4)$ pm, $\alpha = 101.15(2)$, $\beta = 97.77(2)$, $\gamma = 96.96(2)°$, $V = 1954.1 \times 10^6$ pm^3, $\rho_{calc} = 1.09$ g/cm^3, $Z = 2$. Direct methods (SHELXTL), 3753 reflections, $R = 0.065$. Geometry: The four-membered ring is bent at an angle of 18° about the CC diagonal; the aryl groups are rotated through 79 and 80° to the four-membered ring; the angles at P and S in the ring are 84 and 86°, respectively, those at both C atoms 94°; bond lengths [pm]: SC 178/179, PC 181/181, exocyclic: C=S 160, C=P 167; angle at P 99°. Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD 51026, the names of the authors, and the journal citation.

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[8] a) **5**: decomp. 130°C, MS (70 eV): *m/z* 598 ($M^{\oplus}$, 0.07%), 541 ($M^{\oplus} - t$Bu, 0.55), 277 (ArylPH$^{\oplus}$, 71), 264 ($M^{\oplus}$ – ArylPH – *t*Bu, 48), 57 (*t*Bu$^{\oplus}$, 100).—IR (KBr): 2520 (SH), 2420 cm^{-1} (PH).—^{31}P-NMR (32.19 MHz, C_6H_6, standard 85% H_3PO_4): $\delta = -47.1$ (dd, $^2J(PP) = 235$, $J(PH) = 232$ Hz; P=C–*P*), 240.9 (t, $^2J(PP) = 235$, $^1J(PH) = 22$ Hz; *P*=C–P).—^{1}H-NMR (60 MHz, $CDCl_3$): $\delta = 1.25$ (s, *o*-*t*Bu), 1.35 (s, *o*-*t*Bu), 1.50 (s, *p*-*t*Bu), 2.75 (d, $^3J(PH) = 8$ Hz, SH), 6.00 (dd, $J(PH) = 235$, $^3J(PH) = 22$ Hz; PH), 7.35 (s, Aryl).—$^{13}C\{^1H\}$-NMR (20.0 MHz, $CDCl_3$): $\delta = 31$—38 (*t*Bu), 121—156 (aromat.), 175.5 (dd, $J(PC) = 71.7$, $J(PC) = 50.0$ Hz; P=*C*–P).—b) X-ray structure data of **5**: $P2_1/c$, $a = 1060.1(2)$, $b = 1021.7(2)$, $c = 3463.6(9)$ pm, $\beta = 92.29(2)°$, $V = 3748.8 \times 10^6$ pm^3, $\rho_{calc} = 1.06$ g/cm^3, $Z = 4$. Direct methods (SHELXTL), 4736 reflections, $R = 0.059$ ($R_w = 0.048$). Geometry: SCP_2 unit planar and rotated through 81 and 82°, respectively, to the aryl groups. Bond lengths [pm]: SC 176, PC 185, P=C 168. Angle at phosphorus R–P=C 102°, at phosphorus C–P(R)H 100°. Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD 51026, the names of the authors, and the journal citation.

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[11] **7**: $^{31}P\{^1H\}$-NMR (32.19 MHz, C_6D_6): $\delta = 249.1$.—$^{29}Si\{^1H\}$-NMR (13.549 MHz, C_6D_6): $\delta = 14.92$ (s, $SSiMe_3$), 17.85 (d, $^3J(PSi) = 10.7$ Hz, $SSiMe_3$).—^{1}H-NMR (60 MHz, $CDCl_3$): $\delta = 0.58$ (s, $SiMe_3$), 0.80 (s, $SiMe_3$), 1.60 (s, *p*-*t*Bu), 1.82 (s, *o*-*t*Bu), 7.72 (s, aryl).—$^{13}C\{^1H\}$-NMR (20 MHz, $CDCl_3$): $\delta = 1.7$ (d, $^4J(PC) = 5.1$ Hz, $SSiMe_3$), 2.7 (s, $SSiMe_3$), 31.4 (s, C–*C*/Me)$_3$), 32.6 (d, $^4J(PC) = 6.9$ Hz, C=CH_3), 34.9 (s, *C*–CH_3), 37.9 (s, *C*–CH_3), 121.7 (s, C3), 139.4 (d, $J(PC) = 60.8$ Hz, C1), 150.3 (s, C4), 153.0 (d, $^2J(PC) = 1.7$ Hz, C2), 168.5 (d, $J(PC) = 69.7$ Hz, P=*C*).

Insertion of Platinum into the Sulfur-Nitrogen Bond of a 1,2,4-Thiadiazole: Synthesis of a Six-membered Metallaheterocycle**

By *Herbert W. Roesky**, *Hartmut Hofmann*, *Peter G. Jones*, and *George M. Sheldrick*

Dedicated to Professor Gerhard Fritz on the occasion of his 65th birthday

The importance of platinum coordination compounds has increased enormously in recent years, particular interest being attached to their use in homogeneous catalysis and in cancer therapy[1].

Ethenebis(triphenylphosphane)platinum(0) reacts with 1,2,4-thiadiazole-3,5-dicarbonitrile **1**, which is readily accessible from cyanogen and sulfur[2,3], with formation of

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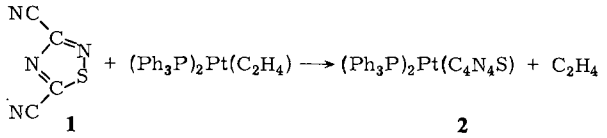
the chelate complex **2**, a complex containing a novel C_2N_2SPt heterocycle.



1 **2**

Insertion of Pt takes place at the SN-bond of **1**. Similar products are also formed on reaction of 1,2,5-thiadiazoles and 1,2,5-selenadiazoles with the Pt^0 complex[4].

The reaction **1**→**2** proceeds smoothly in high yields at room temperature[5]. The compound **2** is sensitive neither to oxygen nor to hydrolysis. On recrystallization[5], solvent molecules are incorporated into the crystal lattice, but are easily given up again. The IR spectrum of **2**[5] shows an absorption band at 2230 cm^{-1} in the C≡N stretching vibration region; this is not observed in the spectrum of **1**. The X-ray structure analysis confirms the presence of a six-membered ring (Fig. 1).

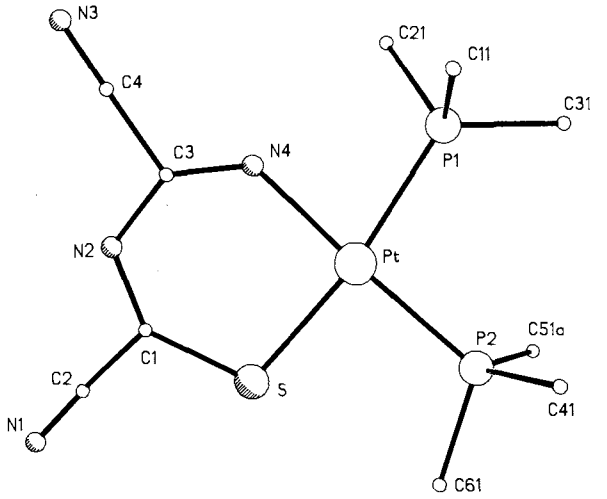


Fig. 1. Structure of the platinum complex **2** in the crystal. (For the sake of clarity, only the first carbon of each phenyl ring is shown.) Space group $P\bar{1}$, $a=1002.0(3)$, $b=1294.2(3)$, $c=1794.7(5)$ pm, $\alpha=96.24(2)$, $\beta=101.98(2)$, $\gamma=103.30(2)°$, $Z=2$; $R=0.050$ for 6828 absorption-corrected reflections with $F>4\sigma(F)$, $Mo_{K\alpha}$ radiation, $2\theta_{max}=52°$. The refinement was rendered difficult by the fact that the asymmetric unit contains 1.5 disordered molecules of dioxane and that a phenyl ring is disordered. Important bond lengths [pm] and angles [°]: Pt–S 229.2(5), Pt–P1 231.1(4), Pt–P2 230.8(4), Pt–N4 201.6(8), S–C1 172(1), C1–N2 130(2), N2–C3 140(1), C3–N4 126(1); P1–Pt–P2 98.5(3), P1–Pt–N4 78.4(4), P2–Pt–S 89.9(2), N4–Pt–S 93.3(4), Pt–S–C1 106.9(6), S–C1–N2 134(1), C1–N2–C3 120(1), N2–C3–N4 134(1), C3–N4–Pt 128(1). The platinum atom is planar coordinated (largest deviation 7 pm for N4); the chelate ligand (S to N4) is likewise planar; however, the platinum atom deviates about 34 pm from this plane. The angle between the two planes is 12.8°. Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD 50865, the names of the authors, and the journal citation.

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[5] A solution of the ethene-complex $(Ph_3P)_2Pt(C_2H_4)$ (1.04 g, 1.40 mmol) in toluene (15 mL) was added dropwise slowly at room temperature to a solution of **1** (0.19 g, 1.40 mmol) in anhydrous toluene (10 mL). A bright yellow microcrystalline precipitate was formed, which, after 12 h, was filtred off and recrystallized from dioxane or tetrahydrofuran. Orange crystals of **2** (0.95 g, 80% yield) were obtained. IR (Nujol mull): 2230, 1445, 1100, 1025, 740, 695 cm^{-1}.

The in situ Preparation of 2-Sulfidophenolate Ligands by Copper-Catalyzed Oxygen Insertion into Thiophenolates; Crystal Structure of $[PPh_4]_2[Mo_2O_5(SC_6H_4O)_2]$**

By *C. David Garner*, John R. Nicholson,* and *William Clegg*

Recently, the syntheses of several Mo–S–Cu clusters have been reported[1], including that of the complex anion $[MoOS_3(CuCl)_3]^{2\ominus}$[1f,g]. In an attempt to prepare the thiophenolate derivative of this $OMoS_3Cu_3$ core, we treated a solution of $[PPh_4]_2[MoOS_3(CuCl)_3]$ in acetonitrile with KSPh (molar ratio 1:3)[2]. The ensuing reaction appears to be complicated and, so far, the only compound we have been able to characterize is $[PPh_4]_2[Mo_2O_5(SC_6H_4O)_2]$ **1**.

According to the results of an X-ray structure investigation, the anion of **1** (Fig. 1) possesses a crystallographic two-fold symmetry axis passing through the μ-oxide ligand, perpendicular to the Mo–Mo vector. The structure

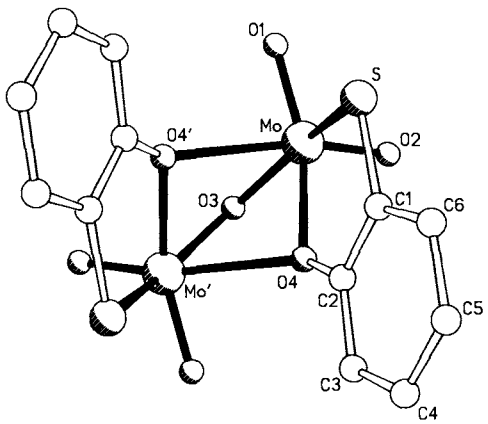

Fig. 1. Structure of the anion of **1** in the crystal, viewed along the two-fold symmetry axis. Space group C2/c, $a=18.317(2)$, $b=12.025(1)$, $c=25.195(3)$ Å, $\beta=108.28(1)°$, $Z=4$, $R=0.039$ for 5104 absorption-corrected reflections with $F>4\sigma(F)$. Key bond lengths [Å]: Mo-O1 1.712(2), Mo-O2 1.699(2), Mo-O3 1.929(2), Mo-O4 2.117(2), Mo-O4' 2.482(2), Mo-S 2.441(1), S-C1 1.763(3), O4-C2 1.346(3) Å. Further details on the crystal structure analysis can be obtained from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, by quoting the depository number CSD 51032, the names of the authors, and the journal citation.

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of the anion closely resembles that of $[Mo_2O_5(o\text{-benzenediolate})_2]^{2\ominus}$[3] and of $[Mo_2O_5(3,5\text{-di-}tert\text{-}1,2\text{-benzenediolate})_2]^{2\ominus}$[4] and possesses two *cis*-dioxomolybdenum(VI) centers bridged by one μ_2-oxido- and two μ_2-*O*-2-sulfidophenolate ligands. The last-mentioned bridges are asymmetric and involve Mo-O distances of 2.117(2) and 2.482(2) Å. The Mo atom has a very distorted octahedral environment of five O and one S donor atoms, with the largest and the smallest bond angles being O2MoO4′ = 167.4(1)° and O3MoO4′ = 67.4(1)°, respectively. The UV/VIS spectrum of $[PPh_4]_2[Mo_2O_5(SC_6H_4O)_2]$ contains two bands of a comparable intensity with $\lambda_{max} \approx 400$ and 350 nm and an absorption of higher intensity with $\lambda_{max} = 297$ nm.

Complexes containing the $(Mo_2O_5)^{2\oplus}$ core usually exhibit two $\nu(Mo-O_{terminal})$ bands in the IR spectrum in the region 910—935 cm^{-1} separated by $\leqslant 20$ cm^{-1}[5]. We therefore propose that the bands observed at ca. 918 and 924 cm^{-1} in the IR spectrum of **1** are due to $\nu(Mo-O_{terminal})$ stretching vibrations. $(Mo_2O_5)^{2\oplus}$ complexes generally absorb at ca. 775 cm^{-1}[5], but although **1** has an absorption at ca. 765 cm^{-1}, its assignment to the ν(Mo-O3-Mo) vibration is complicated by the presence of 2-sulfidophenolate vibrations in this region.

2-Mercaptophenol and its singly and doubly deprotonated anions are of considerable potential interest as ligands, especially as this last form is intermediate between catecholates and *ortho*-benzenedithiolates which form complexes with notable redox properties. However, the chemistry of 2-mercaptophenol derivatives is presently very limited. The study described herein represents the first structural characterization of a complex of the $SC_6H_4O^{2\ominus}$ ligand. The lengths of the C—O and C—S bonds (1.346(3) and 1.763(3) Å, respectively) are taken to indicate that the ligand is present as a dianion rather than in an oxidized form[6]. The singly charged form $HOC_6H_4S^{\ominus}$ has been observed in both a monodentate (through S) and chelating (through O and S) coordination mode in the same FeS cluster compound[7].

The in situ synthesis of the 2-sulfidophenolate ligand appears to involve the aerial oxygenation of benzenethiolate and, given the reaction conditions and known precedents[8], is presumed to be a Cu-assisted process. This approach could offer a potentially attractive alternative to the synthesis[9] of 2-mercaptophenol and related systems.

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[2] $[PPh_4]_2[MoOS_3(CuCl)_3]$ (0.7 g, 0.59 mmol) was dissolved in CH_3CN (ca. 40 mL) under an atmosphere of N_2. Addition of solid KSPh (0.26 g, 1.8 mmol) and stirring overnight at room temperature led to the precipitation of KCl, which was separated off by filtration. Et_2O (ca. 30 mL) was added to the deep red filtrate to give a small amount of black precipitate. Separation of this product by filtration and further addition of Et_2O led to the formation of a black tar. The solution was decanted and more Et_2O added with the same result. After standing at room temperature for ca. 3 weeks, with limited exposure to air, the tar was transformed into a black powder and relatively large deep red crystals had developed. Yield ca. 0.04 g (10%).

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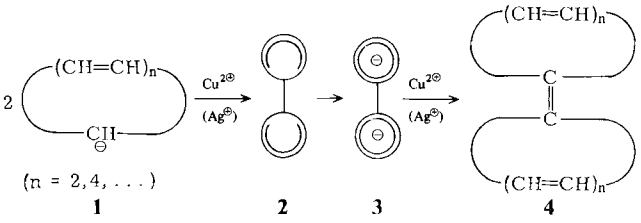
Nonapentafulvalene by Oxidative Coupling of Cyclononatetraenide and Cyclopentadienide**

By *André Escher* and *Markus Neuenschwander**

According to *Doering*, pentafulvalenes[1] can be prepared by reaction of cyclopentadienides with iodine, followed by deprotonation and subsequent oxidation with O_2[2]; however, the atmospheric oxidation is often problematic. We recently reported the oxidative coupling of the Hückel anions **1** with Ag^{I} or Cu^{II} salts[3]. After deprotonation to **3**, the almost quantitatively formed dihydrofulvalenes **2** are again reacted with Ag^{I} or Cu^{II}. This procedure allowed concentration of the reactive pentafulvalene **4** (n = 2)[2] to be increased to a level sufficient for NMR



spectroscopic studies[3]. Recently the same method has been applied to the synthesis of the 2,5-di-*tert*-butylcyclopenta[*a*]pentalenide ion[4]. Here we describe the first synthesis of nonapentafulvalene **12** (9-(2,4-cyclopentadienylidene)-1,3,5,7-cyclononatetraene)[1].

When 1 mmol each of Na-cyclopentadienide (Na-CPD) and *cis,cis,cis,trans*-Na-cyclononatetraenide (Na-CNT)[5] are allowed to react with 2.2 mmol of $CuCl_2$ in 10 mL of tetrahydrofuran (THF) at −50°C, a mixture of the dihydrofulvalenes **5**, **6**, and **7**[6,3] is formed in the ratio 5 : 4 : 1 (yield 85%, calculated from the NMR and GC). In contrast, if 5 mmol Na-CPD and 1 mmol of Na-CNT are coupled using 6.6 mmol $CuCl_2$ in THF, in addition to **5** and **6** (ratio 1 : 4) the product mixture contains only traces of **7**. For the tautomerizations **5** ⇄ **5′** and **6** → **8**, the mixture is treated with aluminum oxide (basic I) at −20°C. The tautomeric 9-(cyclopentadienyl)-1,3,5,7-cyclononatetraenes **5′**

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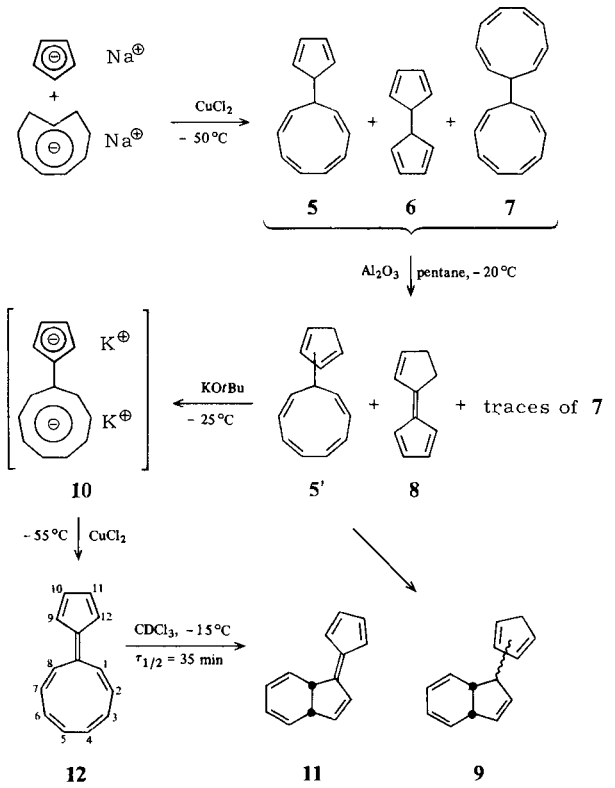
[**] Fulvenes, Fulvalenes, Part 41. This work was supported by the Schweizerischer Nationalfonds (Project No. 2.402-0.82) and by Ciba-Geigy AG, Basel. We thank Dr. *T. Jenny*, Organisch-chemisches Institut, Universität Fribourg (Switzerland) for the high-field NMR spectra.—Part 40: [3].

can be separated by chromatography on silica gel (pentane, −20°C) from the slower moving red dihydrofulvalene **8**[7,3] (70% yield relative to CNT). The structure of **5′** is proved by the spectroscopic data as well as by the cyclization **5′**→**9**, which is rapid at 20°C.



For the synthesis of **12**, a solution of **5′** in THF is deprotonated at −25°C with potassium *tert*-butoxide, whereupon the dipotassium salt **10** precipitates. Reaction with $CuCl_2$ at −55°C affords a red suspension which is worked-up by filtration (silica gel, pentane) and concentrated at −50°C to yield **12** (ca. 30% relative to **5′**).—Nonapentafulvalene **12** is a red hydrocarbon which crystallizes at −50°C, but is so reactive that it has as yet eluded attempts at recrystallization. According to the NMR spectrum, the half-life of the cyclization **12**→**11** is ca. 35 min in $CDCl_3$ at −15°C. Therefore, **12** is even more reactive than nonafulvene[8].

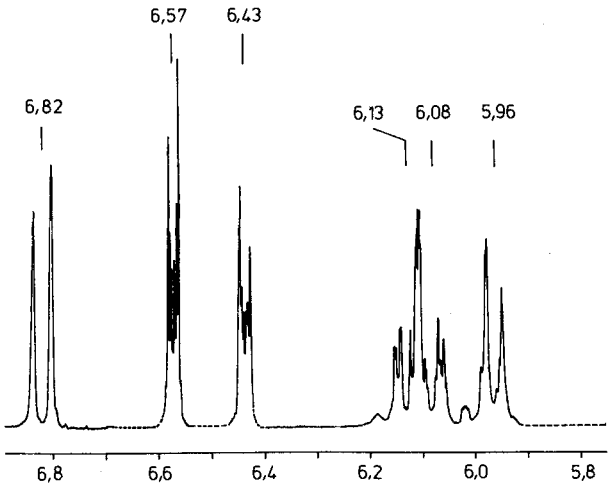


Fig. 1. ^{1}H-NMR spectrum of **12** (360 MHz, [D$_6$]acetone, −40°C; δ values). The breaks in the region $\delta = 5.85$, 6.4, 6.5 and 6.65 signify that the original spectrum contains signals from 9% **11**.

Structure elucidation of **12** is based on the low temperature NMR spectra and on the cyclization **12**→**11**. In the ^{1}H-NMR spectrum (Fig. 1), the ring protons are pairwise equivalent. The key protons 1-H/8-H appear as a doublet at $\delta = 6.82$. Assignment of the remaining protons of the nine-membered ring (2-H/7-H: 6.08; 3-H/6-H: 6.13; 4-H/5-H: 5.96 ppm) follows from decoupling experiments. The centers of the AA′XX′ system of the five-membered ring protons at $\delta = 6.57$ and 6.43 absorb similarly to those of pentafulvalene **4** (n = 2)[3]. In the ^{13}C-NMR spectrum, the signals of the pairwise equivalent C atoms of the nine-membered ring (C^1/C^8: $\delta = 128.0$; C^2/C^7: 133.0; C^3/C^6: 129.5; C^4/C^5: 128.5) appear in the narrow range $\delta = 128$—133 typical for nonpolar nonafulvenes[9]. Furthermore, the positions of the five-membered ring C atoms (C^9/C^{12}: $\delta = 121.2$; C^{10}/C^{11}: 132.2) are very similar to those of pentafulvalene **4** (n = 2) as well as of pentafulvenes[3]. Finally, the disrotatory cyclization **12**→**11**, which is very rapid relative to that of 10,10-bis(dimethylamino)nonafulvene[10] stabilized by electron-donating groups, is consistent with the olefinic character of the cyclononatetraene unit of **12**. The structure of **11** has been confirmed by spectroscopic studies (^{1}H-NMR, ^{13}C-NMR, IR, UV, MS).

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Spiro[2.3]hexanes by $C_4 + C_2$-Coupling**

By *Udo H. Brinker** and *Michael Boxberger*

Cyclobutylidenes **7** are the only small ring carbenes to undergo exclusively *intra*molecular reactions[2,3]. Herein, we report the first *inter*molecular additions of **7** (carbenoid) to olefins for the direct synthesis of spiro[2.3]hexanes **8**.

Diazocyclobutane **2**[4] (IR: $\nu_{CN_2} = 2030\ cm^{-1}$), which is generated from the tosylhydrazone sodium salt **1** in a flash pyrolysis apparatus[5] by sublimation at 140–160°C (ca. 10^{-4} torr), reacts with the styrenes **3a**, **b** to give the 4,5-dihydro-3*H*-pyrazoles **4a**, **b**[6]. The azine **9**[4], methylenecyclopropane **10**, and cyclobutene **11** are formed at the same

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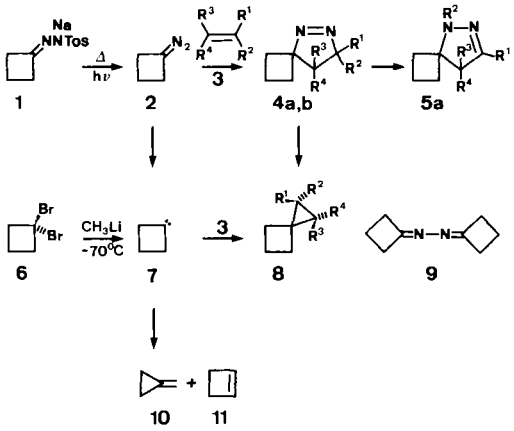

Table 1. Reactions of **2**, **1**, and **6** in the presence of the olefins **3**. Conditions: reaction **2** + **3**: 140°C/10^{-4} torr, −273→0°C. Reaction **1** + **3**: hν, **2d**, RT, Et_2O. Reaction **6** + **3**: CH_3Li/LiBr, Et_2O, −70→0°C.

Educts		R^1	R^2	R^3	R^4	Yields [%] [a]				
						8	**10**	**11**	**4**	**9**
2	**3a**	Ph	H	H	H		17.4 [b]	3.1 [b]	11.0 [c, d]	1.2 [c]
2	**3b**	Ph	Me	H	H		11.3	2.4	4.5	3.9
2	**3c**	Ph	H	H	Me		9.3	1.7	0.3	0.7
2	—						18.6	3.7		2.9
1	**3a**	Ph	H	H	H	35 [c]	[e]	[e]		
1	**3b**	Ph	Me	H	H	11	[e]	[e]		
1	**3c**	Ph	H	H	Me	0.2	[e]	[e]		
6	**3a**	Ph	H	H	H	55	3.7	0.5		
6	**3b**	Ph	Me	H	H	56	[f]	[f]		
6	**3c**	Ph	H	H	Me	57	[f]	[f]		
6	**3d**	Me	H	Me	H	31	[f]	[f]		
6	**3e**	Me	H	H	Me	27	[f]	[f]		

[a] Of compounds isolated. [b] Determination by GC with 2-butyne as internal standard. [c] As for [b], but with biphenyl. [d] On injection into an analytical GC, **4** decomposes completely to **8** (temp.: column 180°C, inj. 220°C). [e] Not analyzed, since **10** and **11** escape during the photolysis. [f] Not determined.

time (see Table 1). **10** and **11** are the typical products of the *intra*molecular reaction of the cyclobutylidene **7** generated from **2**[2a,7]. The 1,3-dipolar cycloaddition of **2** to the styrenes **3a**, **b** to give **4a**, **b** proceeds regioselectively[8]. Apparently, due to the *trans* oriented methyl group in **3c**, there is such a strong steric hindrance in the transition state that the reaction to give **4c**[6] is almost precluded. No spiro[2.3]hexanes **8** are formed under the reaction conditions employed, as could be demonstrated by analytical HPLC in the reaction of **2** with **3a**. Liberation of N_2 from **4a** with formation of **8a** only takes place on heating above ca. 120°C (760 torr). In CCl_4 at 80°C, **4a** rearranges within 10 minutes to give mainly the 4,5-dihydro-1*H*-pyrazole **5a**[6]. Irradiation (Philips HPK 125 W, 20 min) of **4a** in ether affords **8a** in 83% yield. The spirohexanes **8a**—**c**, on the other hand, are obtained via **4** by photolysis of a solution of **1** with styrenes **3a**—**c**.

The organometallic generation of **7** (carbenoid)[7c] at −70°C by reaction of 1,1-dibromocyclobutane **6** with methyllithium in the presence of the olefins **3** affords the spiro[2.3]hexanes **8**[9]. In each case, 5—10% 1-bromo-1-methylcyclobutane[10] is also obtained; this could result from methylation of the organolithium compound generated from **6**. Compound **7** (carbenoid) adds stereospecifically to *cis*- and *trans*-butenes **3d** and **3e**. The competing reactions in **7** to give **10** and **11** take place only to a small extent. The yields of spirohexanes are higher or similar to those of the spiropentanes which are formed by *inter*molecular alkene additions of cyclopropylidenes[2,11], whose *intra*molecular reactions are impaired.

The novel C_4+C_2-coupling presented here opens up a convenient entry to a variety of interesting spiro[2.3]hexanes, which otherwise are only obtainable by circuitous synthetic routes[12].

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[9] Typical procedure: 6.8 mL (7.5 mmol) of a 1.1 M solution of methyllithium/LiBr in ether was added dropwise to a solution of **6** (1.07 g, 5 mmol) and **3a**—**c** (20 mmol) in anhydrous ether (5 mL) at −70°C. After 1 h at −70°C the mixture was allowed to warm within 3 h to 0°C and was then hydrolyzed with 10 mL water. The aqueous phase was washed with 3 × 30 mL ether and the combined extracts were dried over $MgSO_4$ and the solvent evaporated off in a rotary evaporator. **3a**—**c** were removed at room temperature (3 h, 10^{-2} torr), and the residue distilled at 10^{-2} torr (bath temperature 80°C). For spectroscopic characterization, the spirohexanes **8** were purified by GC (**8a**—**c**: 1.2 m, 20% SE 30, 140°C, 120 mL He/min; **8d**, **e**: 3 m, 20% Marlophen, 70°C, 150 mL He/min).
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Synthesis and Characterization of $[(C_5Me_5)Mn(CO)_2(SR)]$; RS Radicals as Ligands**

By *Andreas Winter, Gottfried Huttner*, Laszlo Zsolnai, Peter Kroneck,* and *Margarete Gottlieb*

We report here on manganese complexes in which RS radicals are formally stabilized as ligands. $[CpMn(CO)_2 \cdot thf]$ ($Cp = \eta^5\text{-}C_5H_5$) reacts with thiols RSH in tetrahydrofuran (THF) to afford honey-colored solutions which probably contain complexes of the type $[CpMn(CO)_2(HSR)]$[1]. In the presence of oxygen, these solutions become violet. Deep violet compounds of composition $CpMn(CO)_2SR$ are obtained as the sole products upon chromatographic work-up. More stable complexes are formed via the same reaction sequence from the complex $[Cp^*Mn(CO)_2 \cdot thf]$ **1**[2] ($Cp^* = \eta^5\text{-}C_5Me_5$).

The paramagnetic complexes **2** contain one unpaired electron per molecule[3]. According to the EPR spectrum of

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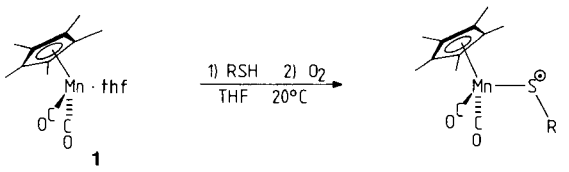

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2a, R = *t*-C$_4$H$_9$ (33%)
2b, R = 2-Adamantyl (29%)

2a (sextet at $g=2.031(9)$, $a^{55}_{Mn}=5.14$ mT), the unpaired electron occupies a molecular orbital (MO) with strong metallic character. In the EPR spectrum of the analogous selenium complex [CpMn(CO)$_2$(SePh)][4] ($g=2.069(9)$, $a^{55}_{Mn}=4.61$ mT) the signals are markedly broadened. Although the superhyperfine splitting by ^{77}Se ($I=1/2$) could not be resolved, the broadening indicates a contribution by selenium to the singly occupied MO (SOMO).

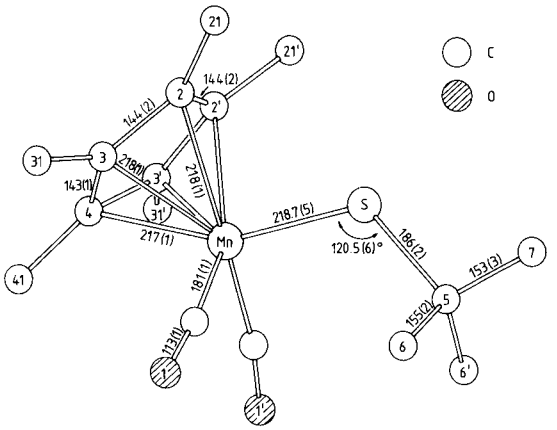

Fig. 1. Structure of the radical complex **2a** in the crystal. Distances in pm (standard deviations in brackets).

Isolated molecules of **2a** occur in the crystal (Fig. 1)[5]. The molecules possess crystallographic mirror symmetry, with the RS ligand lying in the mirror plane of the molecule. The radical complexes are isoelectronic with the radical anions of the carbene complexes [L$_n$M=CR$_2$]$^{\ominus}$[6] and with the aminyl complexes [L$_n$M(HNR)][7], whose bonding behavior has been described in terms of the extended Hückel model by *Sellmann* and *Hoffmann* et al.[8]: Because of the repulsive interaction between the a″-HOMO of the CpMn(CO)$_2$-fragment and the p-orbital of the radical ligand, the SOMO lies at a relatively high energy[7]. This explanation is also consistent with the intense coloration of the complexes **2**[9]. The high energy level of the SOMO[7] also explains the ease with which **2**$^{\ominus}$ can be oxidized to **2** in comparison to other [CpMn(CO)$_2$L] complexes; the reversible reduction of **2** can be detected by cyclic voltammetry[10] (single electron reduction, $E_{1/2}$(**2a**) = −0.98 V and $E_{1/2}$(**2b**) = −0.93 V). The selenium compound [CpMn(CO)$_2$SePh][4] undergoes reversible reduction even more easily ($E_{1/2}$ = −0.55 V). In this way the redox behavior of **2** corresponds to the internal electron transfer postulated for the axial thiolate ligands in cytochrome P450[11].

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[2] A solution of [Cp*Mn(CO)$_3$] (2.74 g, 10 mmol) in 300 mL THF is irradiated for 2.5 h at 7°C (Duran glass apparatus, UV lamp Hanau TQ 150), and is subsequently treated with *t*-C$_4$H$_9$SH (1.7 mL, 15 mmol) for the synthesis of **1a** or with 2-adamantanethiol (2.5 g, 15 mmol) for the preparation of **1b** and stirred for 10 h at 20°C. Air is then passed into the solution for 2 min, producing an instantaneous color change to intense violet. After chromatography at −20°C on silica gel (eluent pentane/diethyl ether 5:1), the crystalline product **2** is obtained. **2a**: Yield: 1.1 g (33%), m.p. = 103°C; **2b**: Yield 1.2 g (29%), m.p. = 122°C. IR spectra (*n*-pentane, [cm^{-1}]): **1a** ν = 1974 (s), 1908 (s); **1b** ν = 1973 (s), 1909 (s). In addition to the molecular peak $M^{\oplus}$, the mass spectrum of **2** exhibits intense signals for the fragments Cp*MnSR$^{\oplus}$, Cp*MnS$^{\oplus}$, Cp*Mn$^{\oplus}$, Cp*$^{\oplus}$, and Mn$^{\oplus}$.

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[9] Between 15000 cm^{-1} and 30000 cm^{-1} two intense absorptions are observed in the electronic spectrum (**1a**: λ = 21277 cm^{-1} (ε = 3060 L mol^{-1} cm^{-1}), 27778 (802); **1b**: 19685 (3870), 25380 (888).

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Thermally and Photochemically Controlled Insertion of Alkynes into Clusters: A Route to Organometallic π-Ligands**

By *Konrad Knoll, Olli Orama,* and *Gottfried Huttner**

Dedicated to Professor Kurt Issleib on the occasion of his 65th birthday

Cluster **1**, readily accessible[2] by oxidation of [μ_3-RPFe$_3$(CO)$_9$H]$^{\ominus}$ **1**[1], reacts upon thermal activation with alkynes to afford almost exclusively **2**, whereas under photochemical conditions **3** is formed.

2 arises via insertion of R′C≡CR″ into one of the P–Fe bonds of **1**. The reaction proceeds remarkably smoothly and regioselectively. Presumably[1] formation of **2** is preceded by scission of a P–Fe bond followed by addition of the nucleophilic Fe$_2$PR group to the alkyne. The observed regioselectivity arises from the formation of the more stable carbanion. Homologues of the expected intermediate $Fe_2R\overset{\oplus}{P}-CR'=\overset{\ominus}{C}R''$ building group have been postulated as ylidic intermediates $R_3\overset{\oplus}{P}-CH=\overset{\ominus}{C}R$[3] and are also known as ligands[4].

The distances and angles in **2**[5] suggest that the almost planar FeCCP moiety be described as a "heterobutadiene" ligand (see Scheme 1). The conformation of the Fe(CO)$_3$ group also corresponds to this illuminative view[6]. In

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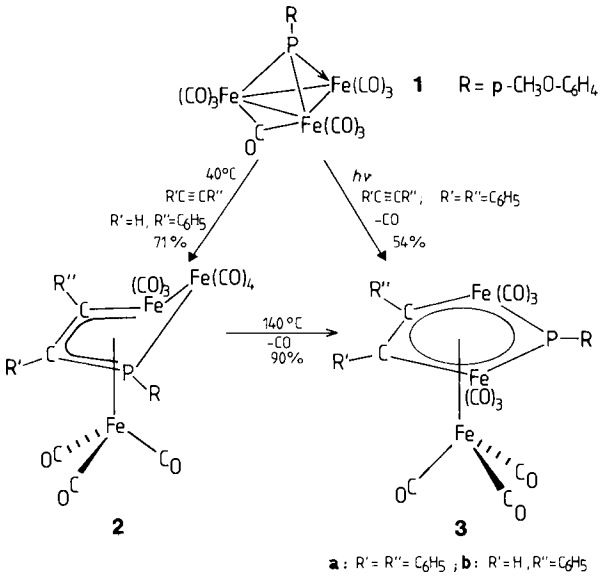
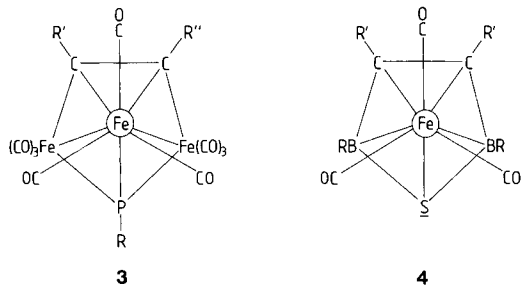


Scheme 1.

terms of *Wade*'s rules[7], **2** is an *arachno*-system which can be converted into the *nido*-cluster **3** upon decarbonylation. **3** forms directly in the photochemical reaction of **1** with alkynes (Scheme 1). In this connection, either the decarbonylation of **1** to afford an unsaturated cluster or the rupture of one of the Fe–Fe bonds can be considered as the initial reaction; in both cases cycloaddition of the alkyne ensues. Formation of **3** formally corresponds to the rare insertion mode of an alkyne into an M–M bond with "parallel" coordination of the alkyne[8].

The conversion of **2** into **3** requires reorganization of the cluster skeleton (Scheme 1), which is typical of carbaboranes. This analogy is also corroborated by the structure of **3**, which contains a planar (deviation ≤ 7 pm), five-membered organometallic heterocycle with adjusted bond lengths, and which, according to *Wade*'s rules[7] and to the criteria stated by *Hoffmann*, is isoelectronic in a wider sense with organoboron 4π-electron ligands such as the thiadiboroles[10] in **4** (Scheme 2).



Scheme 2.

A further notable aspect of the structure of **3** is the incorporation of a trigonal-planar (deviation ≤ 1 pm) "phosphanediyl"[11] into the organometallic heterocycle. With their conjugated organometallic π-ligands, the complexes **2** and **3** are special cases of an as yet small class of compounds.

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[5] **2**: $P2_1/n$, $a=1259(1)$, $b=1423(1)$, $c=1563(2)$ pm, $\beta=107.06(6)°$, $Z=4$, 2730 reflections, $R_1=0.048$; **3a**: $P\bar{1}$, $a=881.7(5)$, $b=1063.2(8)$, $c=1676(1)$ pm, $\alpha=102.21(6)$, $\beta=92.41(5)$, $\gamma=76.01(6)°$, $Z=2$, 3472 reflections, $R_1=0.025$. Distances in the cyclic ligands [pm]: **2**: CC 138(1), CFe 200.5(6), FeFe 283.3(3), FeP 224.0(3), PC 175.8(7); **3a**: CC 141.9(5), CFe 198.9(3), FeP 217.0(2), PFe 216.7(2), FeC 199.3(4). Distances Fe-ring planes: **2**: 177; **3a**: 174 pm. Further details on the crystal structure investigation can be obtained from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, by quoting the depository number CSD 51102, the names of the authors, and the journal citation.
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Crown Ether Complexes of Sulfonium Salts—The X-Ray Crystal Structures of $[PhCOCH_2SMe_2 \cdot [18]Crown\text{-}6]_n[PF_6]_n$ and $[(PhCOCHPhSMe_2)_2 \cdot [18]Crown\text{-}6][PF_6]_2$**

By *Billy L. Allwood, John Crosby, David A. Pears, J. Fraser Stoddart**, and *David J. Williams*

The recent observation[1] that $[Ph_3PMe][PF_6]$ forms a 2:1 complex with [18]crown-6 (18C6) through [C–H···O] hydrogen bonding has led us to investigate whether alkylsulfonium cations also form discrete complexes with crown ethers. Complexation should be favored by the fact that the α-CH group in alkylsulfonium cations, like those in alkylphosphonium ions, are sufficiently acidic to lead to[2] the formation of stable ylides under basic conditions. We were also encouraged in our investigation in the knowledge that, even the neutral molecule Me_2SO_2 forms[3] a crystalline 2:1 complex with 18C6 in which the main source of bonding is undoubtedly [C–H···O] hydrogen bonding. Here, we report on the ability of salts[4] of the ca-

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tions $[1]^{\oplus}$ to $[5]^{\oplus}$ to form crystalline 1 : 1 (polymeric) or 2 : 1 (discrete) complexes with 18C6[5].

$[Ph_2SMe]^{\oplus}$ $[1]^{\oplus}$ $[PhSMe_2]^{\oplus}$ $[2]^{\oplus}$ $[PhCH_2SMe_2]^{\oplus}$ $[3]^{\oplus}$

$[PhCOCH_2SMe_2]^{\oplus}$ $[4]^{\oplus}$ $[PhCOCHPhSMe_2]^{\oplus}$ $[5]^{\oplus}$

In the case of the complexes involving $[4][PF_6]$ and $[5][PF_6]$, the solid state supramolecular structures, as indicated by X-ray crystallography[6], reveal that, although the former exists as a polymeric 1 : 1 structure (Fig. 1), the latter is a discrete 2 : 1 complex (Figs. 2 and 3).

ring B (and B') is partially disordered, thus precluding definitive assessment of its conformational features. It appears that only *one* of the methyl groups, namely $C(19)H_3$, interacts with an 18C6 ring (A), whilst the other 18C6 ring (B) experiences an interaction with the methylene group $C(21)H_2$ only. The methyl group $C(24)H_3$ does not interact with ring B despite apparently being directed towards its center. This may be a contributory factor to the disorder[8] of this ring.

Inspection of space-filling molecular models led us to suspect that replacement of one of the methylene H atoms in $[4]^{\oplus}$ by a bulky group, e.g. phenyl, might discourage polymeric complexation. This is so, as demonstrated by the X-ray crystal structure of the discrete 2 : 1 complex,

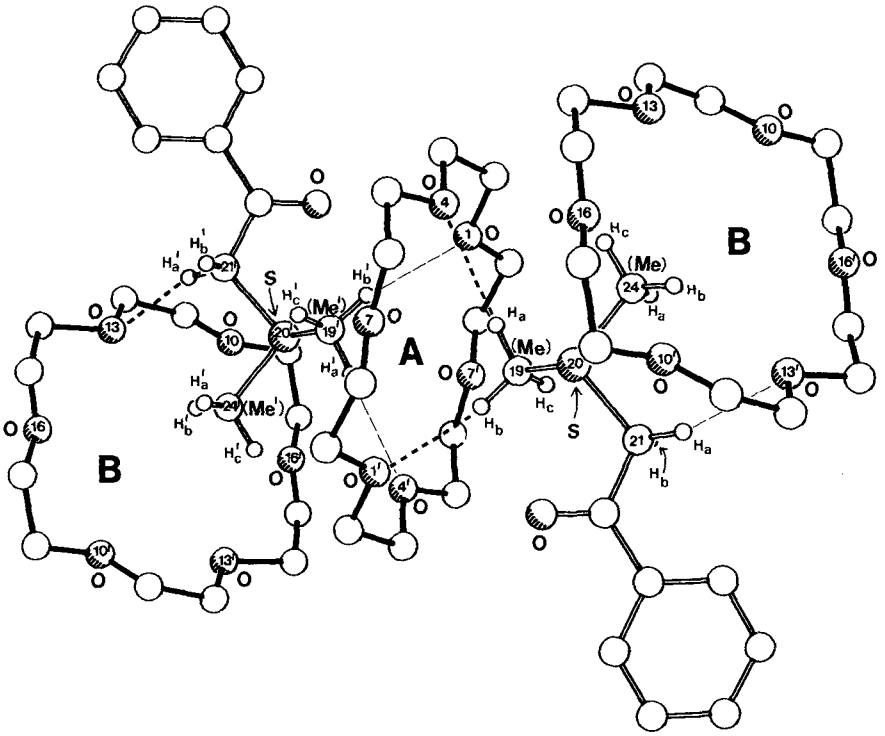

Fig. 1. The supramolecular structure of $[4 \cdot 18C6]_n[PF_6]_n$. Ring A experiences *four*, and ring B *two*, C–H···O contacts of less than 3.4 Å. Distances C···O, H···O [Å] and angles C–H···O [°]: [C(19)···O(1')]H_b: 3.35, 2.43, 163; [C(19)···O(4)]H_a: 3.39, 2.51, 152; [C(21)···O(13')]H_a: 3.30, 2.37, 164. The two shortest contacts between the C(24) methyl group and ring B are 3.29 Å between C(24) and O(16) but the associated H···O distance is 2.94 Å. Me···Me distances [Å]: C(19)···C(19'): 3.88; C(24)···C(24'): 4.53.

Figure 1 shows that the two 18C6 rings in $[4 \cdot 18C6]_n[PF_6]_n$ are situated on crystallographically independent centers of symmetry within the unit cell. The cations $[4]^{\oplus}$ are in general positions sandwiched between the two independent 18C6 rings, which provide different facial relationships to the cations. Ring A adopts a normal all-*gauche* conformation[7] with pseudo D_{3d} symmetry, whilst $[(5)_2 \cdot 18C6][PF_6]_2$ (Fig. 2). The 18C6 ring adopts an all-*gauche* conformation[7] with pseudo D_{3d} symmetry. There is a crystallographic center of symmetry at the center of the ring; all four methyl groups are directed towards the ring. Two methyl groups approach axially towards the center of the ring, whilst the other two bind to the periphery. In both cases, the contacts to the O atoms are long, though in ac-

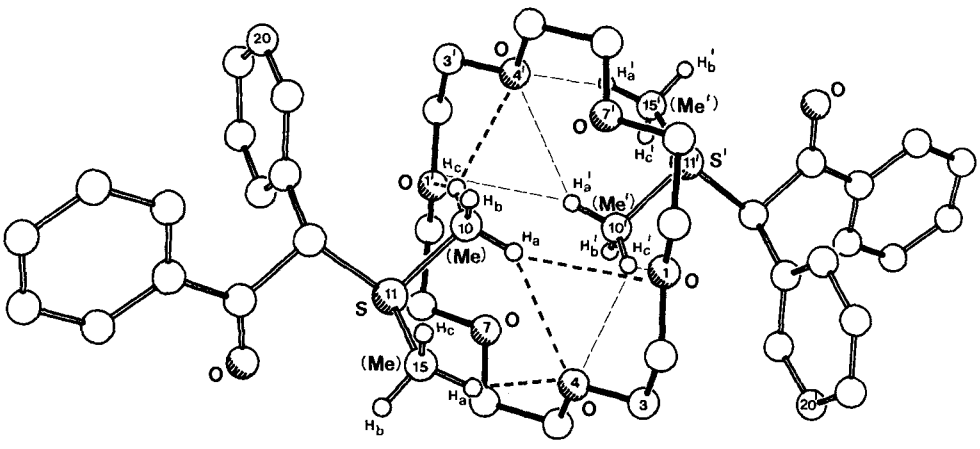

Fig. 2. The supramolecular structure of $[(5)_2 \cdot 18C6][PF_6]_2$. The 18C6 ring experiences *ten* C–H···O contacts of less than or equal to 3.5 Å. Distances C···O, H···O [Å] and angles C–H···O [°]: [C(10)···O(1)]H_a: 3.50, 2.67, 145; [C(10)···O(4)]H_a: 3.41, 2.58, 144; [C(10)···O(1')]H_c: 3.31, 2.53, 139; [C(10)···O(4')]H_c: 3.43, 2.61, 143; [C(15)···O(4)]H_a: 3.38, 2.60, 139. Me···Me distance [Å]: C(10)–C(10') 3.80. The S–C(10) bond is inclined by 53° to the normal to the mean plane of the six-ring oxygen atoms.

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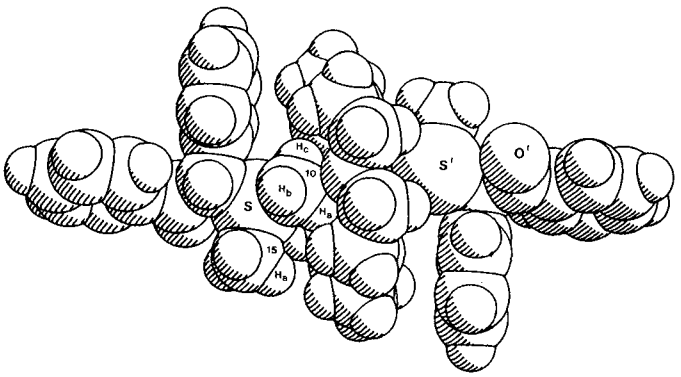

Fig. 3. Space-filling representation of $[(\mathbf{5})_2 \cdot 18C6]^{2\oplus}$.

cord with distances observed for similar interactions[1,3,9]. The two phenyl ring planes are orthogonal to each other (Fig. 3), one adopting a near normal relationship with the 18C6 plane, the other lying nearly parallel (17° between their mean planes). The closest approach by one of the 18C6 H atoms[10] to the mean plane of this phenyl ring is 2.79 Å. The axial methyl groups are tilted and involved in two pairs of bifurcated H bonds to O(1) and O(4), and to O(1') and O(4'). This binding involves simultaneous complexation by each Me group to both near and far oxygen atoms of the 18C6 ring, i.e. a cross between a nesting and perching arrangement[11], as distinct from the conventional perching arrangement observed in $[(Me_2SO_2)_2 \cdot 18C6]$. Although binding differently to the $[Ph_3PMe]^{\oplus}$ ion, the cation $[\mathbf{5}]^{\oplus}$ can still penetrate the 18C6 cavity.

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[6] Crystal data: $[\mathbf{4} \cdot 18C6]_n[PF_6]_n$, triclinic, $a = 10.393(1)$, $b = 11.817(1)$, $c = 12.901(1)$ Å, $\alpha = 116.48(1)$, $\beta = 95.00(1)$, $\gamma = 92.94(1)°$, $U = 1406$ Å^3, space group $P\bar{1}$, $Z = 2$, $\rho_{calc} = 1.39$ g cm^{-3}.—$[(\mathbf{5})_2 \cdot 18C6][PF_6]_2$, triclinic, $a = 10.455(3)$, $b = 10.589(2)$, $c = 13.803(3)$ Å, $\alpha = 75.86(2)$, $\beta = 74.33(2)$, $\gamma = 62.72(2)°$, $U = 1295$ Å^3, space group $P\bar{1}$, $Z = 1$, $\rho_{calc} = 1.37$ g cm^{-3}. Data were measured on a Nicolet R3m diffractometer with graphite monochromated $Cu_{K\alpha}$ radiation and using the ω-scan routine. Both structures were solved by direct methods and refined anisotropically to give, respectively, R values of 0.09 and 0.07 for 3255 and 3025 independent observed reflections [$\theta \leq 55°$, $|F_o| > 3\sigma(|F_o|)$]. Further details of the crystal structure investigation can be obtained from the Director of Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.

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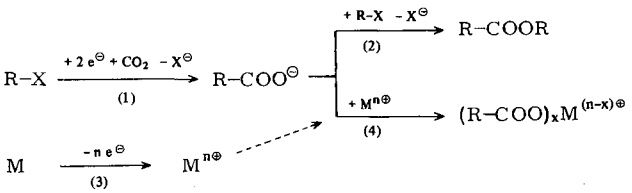
Sacrificial Anodes in the Electrocarboxylation of Organic Chlorides**

By *Giuseppe Silvestri**, *Salvatore Gambino*, *Giuseppe Filardo* and *Antonio Gulotta*

By and large, the electrochemical carboxylation of organic halides has severely limited application, for the carboxylate ion formed cathodically and the still unreacted halide react chemically with each other to form an ester[1-4] [reactions (1) and (2)]. The yields of the carboxylation can therefore not exceed 50% even under the most favorable circumstances.

We wish to report here that in the case of benzylic chlorides it is possible to hinder the esterification by introducing suitable inorganic species into the electrolytic solution. These species are released by sacrificial anodes and substantially improve the yields of the electrocarboxylation. Metal ions arising from the anodic reaction (3) form stable salts with the carboxylate ions which can be isolated on completion of the electrolysis [reaction (4)].



Sacrificial anodes have already been proposed on several occasions for reactions involving carbon dioxide, such as in the production of oxalic acid (with aluminum[5] and zinc[6]) or in the electrocarboxylations of ethylene[7], acenaphthylene[8], and, more recently, a series of thioethers[9]. In all these cases it was possible to perform the syntheses in diaphragm-less cells, and, in many cases, the salts of the carboxylate ions could easily be recovered during the work-up by filtration. The electrocarboxylation of benzylic chlorides described here also has all these advantages.

The metals to be used as sacrificial anodes must have an anodic dissolution potential less positive than that of the oxidation of the organic species present, or to be formed, in the electrolytic medium, and the metal ions released in the electrolytic solution should not to be reduced at the cathode. Aluminum, zinc, and magnesium gave satisfactory results; the most reliable for large-scale electrolyses, how-

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ever, proved to be aluminum. The electrochemical system employed for this study can be schematized as follows:

(Anode) Al / DMF, Bu_4NBr, CO_2, RX / Graphite (Cathode)

(DMF = dimethylformamide). The results obtained with alkyl, benzyl, and aryl chlorides are listed in Table 1.

Table 1. Electrochemical carboxylation of organic chlorides with aluminum anodes [a].

Expt.	Substrate	Amount [g]	Potential [V] [b]	Charge [Coulomb]	Acids obtained	Chemical yield [%]	Current yield [%]
1	1-Chloropropane	0.5	[c]	1300	Butanoic	12.5	11.8
2	1-Chlorobutane	0.5	[c]	1050	Pentanoic	9	9
3	Benzyl chloride	0.9	1.8	1380	Phenylacetic	82.5	82
4	1-Chloro-1-phenylethane	1.64	1.6	2750	2-Phenylpropionic	88	72
5	1-Chloro-1-(3-chlorophenyl)ethane	2	1.8	2210	2-(3-Chlorophenyl)propionic	61.5	61.5
6	1-Chloro-1-(4-chlorophenyl)ethane	2	1.75	2325	2-(4-Chlorophenyl)propionic	88	86
7	1-Chloro-1-(4-isobutylphenyl)ethane	7.5	1.9	7400	2-(4-Isobutylphenyl)propionic	83	75
8	*m*-Dichlorobenzene	1.5	1.7	3900	*m*-Chlorobenzoic	70	35
9	*p*-Dichlorobenzene	2.5	1.65	3300	*p*-Chlorobenzoic	78	49
10	1-Chloronaphthalene	2.5	1.7	4000	1-Naphthoic	57	42

[a] Solvent: Dimethylformamide (50 mL); supporting electrolyte: tetrabutylammonium bromide (1.5 g); cathode: graphite (25 cm^2); anode: aluminum 99.9% (50 cm^2); T: 20 ± 1 °C; CO_2 pressure: 1 atm. [b] Reference system $Ag/AgI/I^{\ominus}$ 0.1 M. [c] Amperostatic experiments, $i = 50$ mA.

Alkyl chlorides were already known to be very poor substrates for carboxylation processes[4], and rather low yields were also found even in this case (entries 1 and 2 in Table 1). The only noticeable effect was the absence of the esters obtained by the other authors. The nature of the side products of the synthesis was not investigated. The best results were obtained with benzyl chlorides (entries 3—7 in Table 1), which gave product and current yields of up to 75—80% at atmospheric pressure, and of up to 90% in tests performed under carbon dioxide pressurized at 20 atm. Among the benzylic chlorides, the α-methyl derivatives (entries 4—7) are of greater interest, for the substituted 2-arylpropionic acids obtained from them are currently used in the pharmaceutical field as anti-inflammatory and antirheumatic agents. The reliability of the synthesis on a preparative scale was tested for the preparation of 2-(4-isobutylphenyl)propionic acid (Ibuprofen) from 1-chloro-1-(4-isobutylphenyl)ethane. The acid was prepared at atmospheric pressure, with 83% product yield and 75% current yield, under the following conditions: 20 g of chloride (20% in DMF), 3.25 g of Bu_4NBr (3%), cathode potential: 1.9 V (vs. $Ag/AgI/I^{\ominus}$ 0.1 M); overall cell voltage = 2.5—3 V; initial current intensity 1 A. After consumption of 19650 coulombs, 1.9 g of unreacted halide (conversion 90.5%) and 15.75 g of the acid were recovered. The preparation of 1 g of acid required 1.2 g of chloride, 0.116 g of aluminum, 0.3 g of DMF, and 0.2 g of Bu_4NBr.

Due to their inactivity towards nucleophilic reagents, aryl halides do not undergo any esterification after the electrocarboxylation. Several examples of electrocarboxylations of aryl chlorides have already been published[10–12]. We have verified that these electrocarboxylations take place in good yields even with sacrificial anodes (entries 8—10 in Table 1).

The controlled potential electrolyses were all performed in diaphragm-less cells with 99.9% aluminum anodes and compact graphite cathodes. The mixing of the solution and the saturation with CO_2 was effected by continuous bubbling of anhydrous CO_2 between the electrodes. The electrolyzed solution was distilled off at reduced pressure and the residue was hydrolyzed at room temperature with diluted HCl, then extracted with ether. The removal of ether after drying gave the acids, which were purified by recrystallization[13].

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Cyclization of 3-Allyloxycarboxylic Acids to Tetrahydrofurans by Kolbe Electrolysis**

By *Matti Huhtasaari, Hans J. Schäfer**, and *Lisa Becking*

Dedicated to Professor Wolfgang Lüttke on the occasion of his 65th birthday

5-Hexenyl radicals cyclize in a 5-*exo*-*trig*-reaction[1] to afford five-membered rings[2]. Recently this addition has been used for the elegant synthesis of carbo-[3] and, particularly, of heterocyclic[4] five-membered rings.

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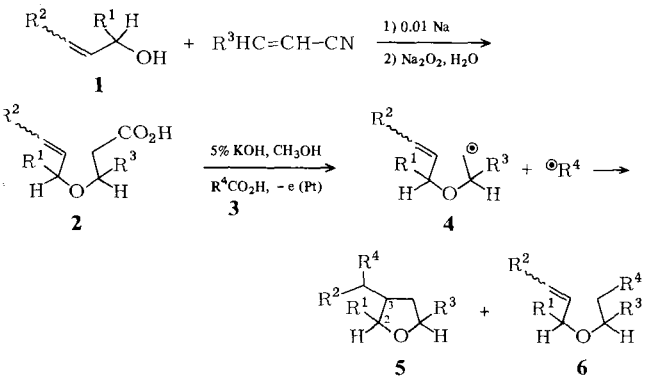
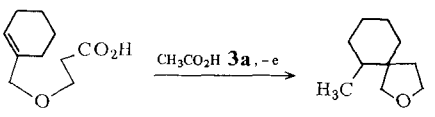
In the mixed Kolbe electrolysis of unsaturated carboxylic acids R–CH=CH–$(CH_2)_n$–CO_2H we found that with n = 4 or 5 substituted cyclopentanes or cyclohexanes were formed as side products[5]. We have now been able to show that this anodic cyclization can be used to convert 3-allyloxycarboxylic acids **2** into substituted tetrahydrofurans **5** (Table 1). 3-Allyloxycarboxylic acids are accessible in 47–80% yield by Michael addition of substituted allyl alcohols **1** to α,β-unsaturated nitriles[6] and subsequent saponification of the nitrile group (alkaline H_2O_2, room temperature)[7].



1 **2** **3** **4** **5** **6**

The 3-substituent can be varied at will by the choice of acid R^4CO_2H **3**; in previous radical heterocyclizations this was not possible, since, because of the radical chain addition, R^4 was usually[9] hydrogen.

With allyl ethers such as **7** the reaction leads to spirotetrahydrofurans such as **8** (molar ratio **7** : **3a** = 1 : 3.5, 23% as determined by gas chromatography).



7 **8**

Procedure:

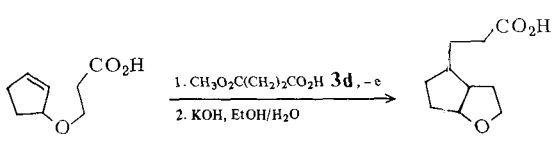
5ed: **2e** (0.5 g, 3.2 mmol) and **3d** (2.1 g, 16 mmol) are dissolved in 25 mL methanol, partially neutralized with 5% KOH, and electrolyzed using platinum electrodes (3 cm^2/electrode) in an undivided cell using a current density of $i = 360$ mA/cm^2 at 40 °C until pH 8 was reached. The mixture was worked-up with brine (20 mL water and 10 g NaCl) and then extracted for 12 h with ether. After evaporation of the ether, the esters are saponified by refluxing for 3 h with KOH (molar ratio 1 : 2) in 30 mL ethanol and 15 mL water. After the usual work-up procedure, **5ed** is separated from the succinic acid by extraction with refluxing petroleum ether; kugelrohr distillation gives: 0.24 g (41%) **5ed** (b.p. = 135 °C/0.03 torr).—IR: $\tilde{\nu}$ = 3500–2500 (OH), 1760–1740 (C=O) cm^{-1}.—^{1}H-NMR ($CDCl_3$): δ = 10.8 (s, 1H), 4.45 (m, 1H), 3.9–3.5 (m, 2H), 2.35 (t, 2H), 2.2–1.5 (m, 9H), 1.25 (m, 1H).—MS (methyl ester) (70 eV): *m/z* 198 (5%, $M^{\oplus}$), 111 (100%, $M^{\oplus} - CH_2CH_2CO_2CH_3$).

Table 1. Mixed Kolbe electrolysis of 3-allyloxycarboxylic acids **2** with carboxylic acids **3** to give substituted tetrahydrofurans **5** (and ethers **6**).

No.		Carboxylic acids					**2** : **3**	Products			
		R^1	R^2	R^3		R^4	[a]		Yield [%]		Yield [%]
1	**2a**	H	H	H	**3a**	CH_3	1 : 4	**5aa**	36 [b]	**6aa**	25 [b]
2	**2b**	H	CH_3 [c]	H	**3a**	CH_3	1 : 3	**5ba**	42 [b]	**6ba**	24 [b]
3	**2c**	H	H	CH_3	**3a**	CH_3	1 : 3	**5ca**	71 [b]	**6ca**	13 [b]
4	**2d**	CH_3	H	CH_3	**3a**	CH_3	1 : 4	**5da**	70 [b]	**6da**	1 [b]
5	**2d**	CH_3	H	CH_3	**3b**	$(CH_2)_4CH_3$	1 : 4	**5db**	52		
6	**2d**	CH_3	H	CH_3	**3c**	$(CH_2)_4CO_2CH_3$	1 : 4	**5dc**	41		
7	**2e**	$-(CH_2)_2-$		H	**3a**	CH_3	1 : 3.5	**5ea**	65 [b]	**6ea**	9 [b]
8	**2e**	$-(CH_2)_2-$		H	**3d**	$(CH_2)_2CO_2CH_3$	1 : 4	**5ed**	41 [d, f]		
9	**2e**	$-(CH_2)_2-$		H	**3e**	$CH_2CO_2CH_3$	1 : 5	**5ee**	41 [e, f]		
10	**2f**	$-(CH_2)_3-$		H	**3a**	CH_3	1 : 3	**5fa**	53 [b]		

[a] Molar ratio. [b] Yield determined by gas chromatography. [c] *trans*-Isomer. [d] $R^4 = (CH_2)_2CO_2H$. [e] $R^4 = CH_2CO_2H$. [f] After saponification.

Formation of the products can be accounted for as follows: The potassium salt of **2** undergoes anodic decarboxylation to give the alkyl radical **4**, which then adds intramolecularly to the double bond and couples with the radical $^{\odot}R^4$ of the co-acid to afford **5**. At the same time, before cyclization **4** combines with $^{\odot}R^4$ to yield the allyl ether **6**. Methyl groups (R^1, $R^3 = CH_3$), which in the product are located directly on the ring, promote the cyclization via the *gem*-dialkyl effect[8] (Table 1, Nos. 3, 4). In the combinations **2e** and **3a**, **d**, **e** or **2f** and **3a** two diastereomers are formed in the ratio 3 : 2 or 1 : 1 (Nos. 7–10). Because of the geometry of the transition state in the cyclization, the tetrahydrofuran and cyclopentane, or cyclohexane rings are constrained to be *cis*-annelated. Furthermore, steric factors in the radical combination make it likely that the substituent in the predominant diastereomer of **5ea**, **5ed** and **5ee** adopts an *exo*-position.



2e **5ed**

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$[Ni_8(\mu_4\text{-}PPh)_6(PPh_3)_4]$ and $[Ni_9(\mu_4\text{-}PPh)_6(PPh_3)_4]$; Clusters with Coordinatively Unsaturated Ni-Atoms**

By *Dieter Fenske**, *Johannes Hachgenei*, and *Friedhelm Rogel*

Dedicated to Professor Gerhard Fritz on the occasion of his 65th birthday

Recently we reported a straightforward method for the preparation of nickel clusters. For this purpose, $NiCl_2$ is allowed to react with $PhP(SiMe_3)_2$ in the presence of PPh_3. Upon addition of CH_3COCl, a mixture of $[Ni_8(CO)_4(PPh)_6(PPh_3)_4]$ **1** and $[Ni_8Cl_4(PPh)_6(PPh_3)_4]$ **2** is obtained[1]. The mechanism of formation of **1** and **2** remained unknown. Apparently **1** is formed first and then reacts with further CH_3COCl to afford **2**. In accord with this, $[Ni_8Br_4(PPh)_6(PPh_3)_4]$ is obtained from **1** and CH_3COBr. To throw some light on the reactive intermediates, we covered the reaction solution of $NiCl_2$, PPh_3, and $PhP(SiMe_3)_2$ with a layer of heptane. In this way, the extremely oxygen-sensitive crystalline compound $[Ni_8(PPh)_6(PPh_3)_4]$ **3** is isolated. This compound is also obtained by reducing **2** with Na/Hg[2].

$$NiCl_2 \xrightarrow[PhP(SiMe_3)_2]{PPh_3} \underset{\mathbf{3}}{[Ni_8(PPh)_6(PPh_3)_4]} \xleftarrow[Hg]{Na} \underset{\mathbf{2}}{[Ni_8Cl_4(PPh)_6(PPh_3)_4]}$$

The IR spectra of **2** and **3** are identical; like **2**, compound **3** is also paramagnetic. This manifests itself in the ^1H-NMR spectrum of **3**, where the phenyl protons have a chemical shift $\delta = 0.31-11.09$. No P resonance signal was observed in the ^{31}P-NMR spectrum of **3**.

According to the results of the crystal structure analysis (Fig. 1), **3** consists of a distorted Ni_8-cube, each face of which bears a μ_4-PPh ligand. Ni1, Ni3, Ni6, and Ni7 are tetrahedrally coordinated by the P atoms of the PPh_3- and μ_4-PPh ligands. In contrast, Ni2, Ni4, Ni5, and Ni8 are bound only to the P atoms of three μ_4-PPh ligands and are, therefore, coordinatively unsaturated. This means that the cluster contains Ni atoms with 18 (Ni1, Ni3, Ni6, and Ni7) and with 16 (Ni2, Ni4, Ni5, and Ni8) valence electrons. With 112 valence electrons, **3** has eight electrons less than one would expect for a stable M_8-cluster[3].

In both **1** and **2** a regular Ni_8 cube is found. As a consequence of the electron deficiency, **3** is distorted. This is expressed by the fact that the Ni atoms with 16 valence electrons have a nonbonding distance of 323—325 pm. In contrast, this distance (384—387 pm) is considerably larger between the Ni atoms with 18 valence electrons. In this way the (Ni–Ni–Ni) bond angles of the cube are distorted: 79.2—80°, (Ni1, Ni3, Ni6, Ni7) and 99.2—100.1° (Ni2, Ni4, Ni5, Ni8). The different distances between the Ni atoms are expressed, moreover, by the bond lengths to μ_4-P. Furthermore, the Ni–Ni distances of 251—254 pm are considerably shorter than in **1** (265—268 pm) and **2** (259—262 pm).

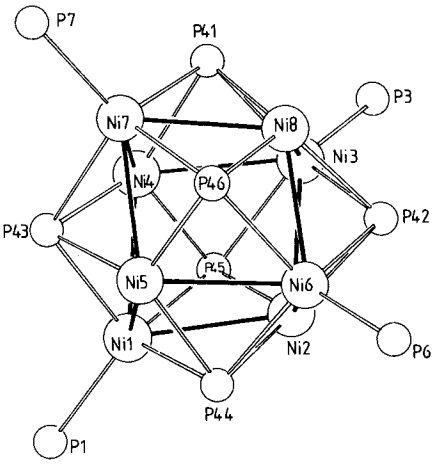

Fig. 1. Structure of the cluster **3** in the crystal (without phenyl groups). P1, P3, P6, P7 and P41—P46, respectively, are the P atoms of the PPh_3 and PPh ligands. Crystals from toluene; **3** crystallizes with 1 mol toluene per formula unit, C_c, $Z=4$, $a=1583.2(8)$, $b=2768.5(10)$, $c=2509.5(11)$ pm, $\beta=99.82(4)°$ (180 K). $\mu(Mo_{K\alpha})=15.3$ cm^{-1}. Syntex R3, up to $2\theta=35°$, 5915 independent reflections, 3534 of which with $I>2\sigma(I)$, empirical absorption correction. Patterson methods, all atoms (without H) refined isotropically, phenyl groups treated as rigid groups (C–C 139.5 pm). $R_1=0.088$, $R_2=0.083$. Selected distances [pm]:Ni–Ni 251—254(1), Ni2,4,5,8-μ_4-P 212—216(1), Ni1,3,6,7-μ_4-P 224—228(1), Ni1–P1 221(1), Ni3–P3 220.3(10), Ni6–P6 218.0(11), Ni7–P7 218.4(12); selected bond angles [°]: Ni(18e)–Ni(16e)–Ni–(18e) 99.2—100.1(2), Ni(16e)–Ni(18e)–Ni(16e) 79.2—80.0(2), Ni(18e)–(μ_4-P)–Ni(18e) 115.2—118.5(6), Ni(16e)–(μ_4-P)–Ni(16e) 97.0—99.2(5), Ni(18e)–(μ_4-P)–Ni(16e) 68.8—71.2(4) [4].

In **3**, the tricoordinated Ni atoms (Ni2, Ni4, Ni5, Ni8) are surrounded in a crown-like manner by the six phenyl groups of the PPh_3 and PPh ligands. In the solid state this arrangement results in the formation of canals having a diameter of 400—500 pm, as illustrated in Figure 2 for the example of the coordination gap at Ni5.

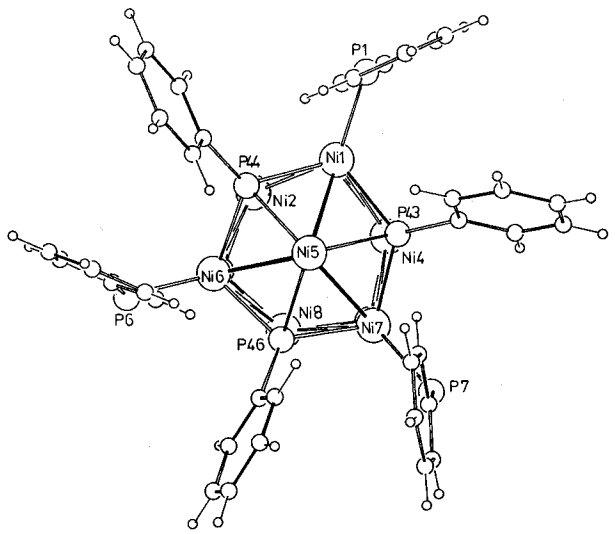

Fig. 2. Structure of the coordination gap at Ni5 in **3**. For reasons of clarity the remaining pheny groups are not shown.

The reason for the stability of **3** is possibly that only molecules of suitable size can be coordinated by Ni2, Ni4, Ni5, and Ni8. In accord with this, compound **3** reacts in

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tetrahydrofuran (THF) with CO, NO, and RNC to form $[Ni_8X_4(PPh)_6(PPh_3)_4]$ (X = CO, NO, t-C_4H_9NC). These compounds are also obtained when **2** is reduced with sodium amalgam in the presence of CO, NO, and RNC.

Reduction of a solution of **2** and $NiCl_2$ in THF with sodium amalgam affords the paramagnetic compound $[Ni_9(PPh)_6(PPh_3)_4]$ **4**.

$$\underset{\mathbf{2}}{[Ni_8Cl_4(PPh)_6(PPh_3)_4]} \xrightarrow[NiCl_2]{Na/Hg} \underset{\mathbf{4}}{[Ni_9(PPh)_6(PPh_3)_4]}$$

In the ^{31}P-NMR spectrum of **4** resonances at $\delta = 430$ (μ_4-PPh) and 25.1 (PPh_3) are observed. For the phenyl protons, signals are found between $\delta = 0.04$ and 7.59. According to the results of the crystal structure analysis, **4** contains a distorted Ni_8-cube to which a further Ni atom (Ni9) is bound[4].

Within the limits of the standard deviations, the bond lengths in **4** are identical with those of the corresponding bonds in **3**. The distance Ni5–Ni9 of 268.6(2) pm lies in the region of a Ni–Ni single bond[5].

The electron balance of **4** indicates that both the Ni_8 and Ni_9 clusters contain less electrons than would be expected from the noble gas rule.

Comparison of the structures of **3** and **4** indicates that the latter arises formally by occupation of a coordination gap in **3** by Ni9. Thereby, the structure of the gap shown in Figure 2 is not changed. The stability of **4** possibly arises because Ni9 participates in weak interactions with the π electrons of the adjacent phenyl groups (distances of Ni9 to the nearest C atoms: 326–380 pm). We have not yet been able to incorporate other metal atoms into **3**.

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[2] Procedures: **3**: Anhydrous $NiCl_2$ (9.72 g, 0.075 mol) and PPh_3 (20 g, 0.076 mol) are suspended and dissolved, respectively, in 250 mL THF and treated with $PPh(SiMe_3)_2$ (20 mL, 0.075 mol). After 4 d, unreacted $NiCl_2$ is filtered off and the solvent removed. The residue is washed with *n*-pentane to remove unreacted $PPh(SiMe_3)_2$ and PPh_3, and the product is recrystallized from toluene.—**4**: A solution of **2** (1 g, 0.43 mmol) and $NiCl_2$ (0.45 g, 3.4 mmol) in 100 mL THF is allowed to react with sodium amalgam (0.2 g Na in 40 g Hg) (color change within 1 h from green to brown and back to green). After 1 d the mixture is filtered off and the solvent removed. The residue is taken up in toluene and covered with a layer of *n*-pentane. **4** crystallizes out at the phase boundary.

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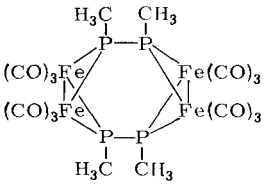
[5] J. A. Jarvis, R. H. B. Mais, P. B. Owston, D. T. Thompson, *J. Chem. Soc. A 1970*, 1867; H. Vahrenkamp, V. A. Uchtmann, L. F. Dahl, *J. Am. Chem. Soc. 90* (1968) 3273; G. Huttner, H. Lorenz, *Chem. Ber. 107* (1974) 996.

$[(CO)_3FePCH_3]_4$, an Organometallic Analogue of Octabisvalene**

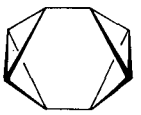
By *Rajib Lal De* and *Heinrich Vahrenkamp**

Dedicated to Professor Kurt Issleib on the occasion of his 65th birthday

According to *Hoffmann*'s isolobal relationship[1], the $(CO)_3Fe$ unit is related to the fundamental species BH or $CH^{\oplus}$ and the ER (E = P, As) unit, to NH or $CH^{\ominus}$. Complexes of the composition $[(CO)_3FeER]_n$ should therefore exhibit a relationship to the hydrocarbons $(CH)_{2n}$. We have previously been able to confirm this for the tetrahedrane analogue $[(CO)_3FeP{t}C_4H_9]_2$[2] and for the cubane analogue $[(CO)_3FeAsCH_3]_4$[3]. The novel Fe_4E_4 isomer $[(CO)_3FePCH_3]_4$ **1**, an analogue of the as yet unknown hydrocarbon octabisvalene **2**[4], represents the third example of a relationship of this type.



1



2

The orange-red tetranuclear complex **1** is formed in 8% yield, analogously to $[(CO)_3FeP{t}C_4H_9]_2$[2], by deprotonation of $[(CO)_3Fe{-}PHCH_3]_2$ with methyllithium in ether, subsequent oxidation with 1,2-dibromomethane, and chromatography on silica gel; complexes of the type $[Fe_2(CO)_6(PR_2)_2]$ also form. According to the IR spectrum (cyclohexane: $\nu = 2048$ (s), 2032 (s), 1989 (s), 1973 (m) cm^{-1}), **1** is an $[Fe_2(CO)_6(\mu\text{-}PX_2)_2]$-derivative. The ^1H-NMR spectrum (broad singlet at $\delta = 1.07$ in C_6D_6) and EI mass spectrum of **1** ($M^{\oplus} - CO$, 100%) are equivocal, and for its identification we therefore resorted to a crystal structure analysis[5] (Fig. 1).

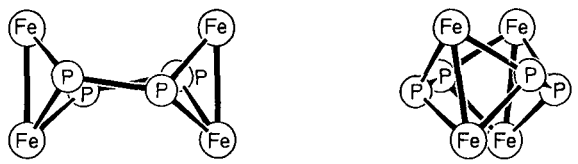


Fig. 1. Two views of the framework of **1** in the crystal [5]. Distances: Fe–Fe 261.8(1), Fe–P 221.0–223.7(2); P–P 222.6(4), P···P 279.6(4) pm.

The molecule **1** consists of two $[Fe_2(CO)_6(\mu\text{-}PRX)_2]$ moieties; a twofold axis passes through the middle of the molecule and runs roughly in the direction of the Fe–Fe bonds. Within the molecular halves all bond lengths and angles are normal[6]. The linking P–P bonds (223 pm) correspond to a single bond length. In contrast to the R_2P_2 ligands in $[(CO)_3FeP{t}C_4H_9]_2$[2], the R_2P_2 ligands in **1** *cannot* be designated as diphosphene moieties. Figure 1 indicates that the framework of **1** is highly symmetric and ought to be similar to that of octabisvalene.

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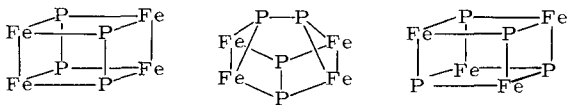
The tetrahedrane framework with R = *t*Bu and the octabisvalene framework with R = CH_3 presumably form because of steric reasons. Whereas the hydrocarbon **2** is highly strained, the arrangement in **1** is largely strain-free, based on the intermolecular contact distances.

With other residues R the occurrence of not only the tetrahedrane- but also the octabisvalene-analogous $[(CO)_3FePR]_x$ complexes and, possibly, their interconversion is to be expected.



3 **4** **5**

Further $[(CO)_3FePR]_4$ isomers with the molecular frameworks **3**, **4**, and **5** are conceivable: these already exist in the form of the hydrocarbons cubane and cuneane and as the As analogue of **5**. The skeletons of **3** and **4** could arise from **1** without rupture of the P–P bonds, whereas formation of framework **5**, which is to be expected on the basis of the P–As analogy, presumably has a higher energy of activation. It is conceivable that compounds of the as yet unknown $[(CO)_3FePR]_3$-type are also formed in such reactions.

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1, 93474-10-3; **2**, 35434-67-4; $[(CO)_3FePHCH_3]_2$, 38890-24-3.

[1] R. Hoffmann, *Angew. Chem. 94* (1982) 725; *Angew. Chem. Int. Ed. Engl. 21* (1982) 711.
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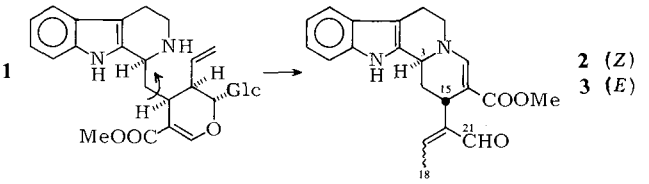
[5] C2/c, $a = 1085.6(1)$, $b = 1624.5(2)$, $c = 1500.0(7)$ pm, $\beta = 102.25(3)°$, $Z = 4$, 2289 reflections, $R = 0.037$. Further details on the crystal structure analysis can be obtained from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, by quoting the depository number CSD 50940, the names of the authors and the journal citation.
[6] W. Clegg, *Inorg. Chem. 15* (1976) 1609.

Total Synthesis of the Indole Alkaloid Vallesiachotamine

By *Dietrich Spitzner** and *Ernest Wenkert*

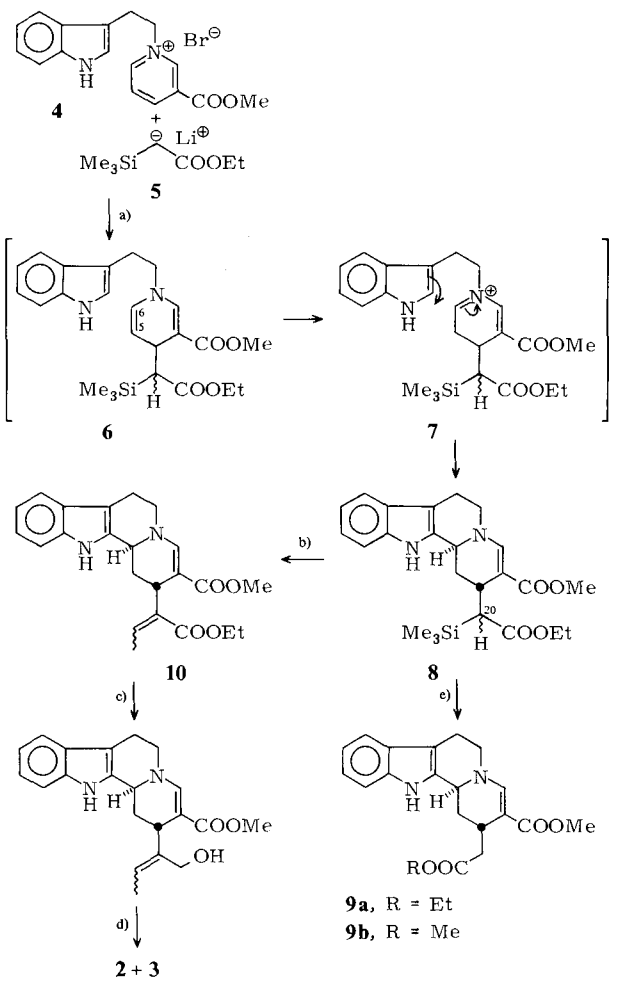
Dedicated to Professor Wolfgang Lüttke on the occasion of his 65th birthday

Tryptamine and secologanin are biosynthetic precursors of a vast number of structurally different indole alkaloids[1], some of which exhibit interesting biological activity. Extensive evidence has established the initial formation of strictosidine **1**[2], which in vivo can then undergo numerous rearrangements and cyclizations. Vallesiachotamine **2** and its (*E*)-isomer isovallesiachotamine **3** are "early" end products formed from **1**, which can also be formed by mild in vitro hydrolysis[3]. As early as 1966, *Djerassi* et al. obtained **2** (presumably as a mixture with **3**) as a minor constituent (0.001%) of the alkaloid fraction from the Peruvian plant *Vallesia dichotoma Riuz et Pav* (family, Apocynaceae)[4].



2 (*Z*)
3 (*E*)

In the course of investigations of the addition of silicon-stabilized anions to pyridinium salts[5], we have now found a short, convergent synthetic route to **2** (Scheme 1). Reaction of the ester enolate **5**[6] with the pyridinium salt **4**, readily accessible from tryptophyl bromide and methyl nicotinate, affords the tetracycle **8** (mixture of epimers). This addition proceeds similarly to that of malonic ester anion to pyridinium salts: addition to 1,4-dihydropyridine **6**,



Scheme 1. a) 1. THF −50 to 23 °C; 2. benzene/HBr; 47%; b) 1. LDA, −78 °C; 2. acetaldehyde, −78 to 23 °C; 68.5%; c) $LiAlH_4$, THF, 5 °C; 81%; d) 1. activ. MnO_2, CH_2Cl_2, 23 °C; 2. prep. TLC (silica gel G/ether); 60%; e) KF in MeOH; quantitative.

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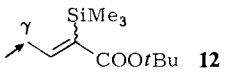
whose 5,6-double bond is protonated to give the intermediate iminium salt **7**. Compound **7** can cyclize to the quinolizidine derivative **8** via a Pictet-Spengler reaction, a reaction which has already proven valuable in yohimbine syntheses[7]. At pH 3 we observed exclusively 1,4-addition of **5** to **4** and practically no desilylation. As expected, **8** is readily desilylated by potassium fluoride in methanol to furnish the diester **9a**, whose ^{1}H- and ^{13}C-NMR spectra—except for the ester group (Et instead of Me in **9a**)—are in accord with those of the known **9b**[8,9]. In this way, the stereochemistry of **8**, with the exception of the relative configuration at C^{20}, which for our synthesis of **2** (and **3**) is unimportant, could be determined: 3-H and 15-H are *trans*-orientated. In the subsequent Peterson olefination [double deprotonation with lithium diisopropylamide (LDA) and reaction with acetaldehyde] no nitrogen protecting group was required, and we obtained the α,β-unsaturated esters **10** in 68.5% as a (*Z,E*)-mixture (3 : 1). Controlled reduction of **10** with lithium aluminum hydride in tetrahydrofuran (THF) yielded the dihydrovallesiachotamines **11**, which were oxidized to **2** and **3** with activated manganese dioxide. Our synthetic **2** (and **3**) was found to be identical (except for its chiroptical properties) with an authentic sample from plant cell cultures[10]. In the ^{1}H-NMR spectrum of **2**, we observed a weak nuclear Overhauser effect (NOE) between the aldehyde proton and C-18 proton, which suggests that the 19,20-double bond has a (*Z*)-configuration.



12

An attempt to prepare **2** by direct addition of the anion of **12**[11] to **4** failed, due to exclusive γ-addition.

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[8] Procedure for **8**: A freshly prepared solution containing 2.1 equivalents of anion **5** (obtained with LDA at −78 °C in THF) is added dropwise to a suspension of **4** in anhydrous THF at −50 °C under an inert gas atmosphere. The salt **4** dissolves during the reaction. The reaction mixture is allowed to warm to room temperature over 2 h, acidified (pH 3) with a solution of HBr in benzene, and stirred for 1 h. After removal of solvent in vacuo, the residue is dissolved in CH_2Cl_2 and filtered through silica gel. Mixed crystals of both epimers of **8** (47%) crystallize from the concentrated filtrate. ^{13}C-NMR of a pure epimer with m.p. = 173 °C (62.88 MHz, TMS, $CDCl_3$): δ = 174.9 (s, ester-C), 168.7 (s, ester-C), 146.7 (d), 136.4 (s), 133.1 (s), 126.9 (s), 122.1 (d), 119.8 (d), 118.1 (d), 111.1 (d), 108.2 (s), 96.7 (s), 60.1 (t), 51 (t), 50.6 (q), 48.3 (d), 44.3 (d), 33.9 (t), 29.2 (d), 22.1 (t), 14.6 (q), −1.5 (q).
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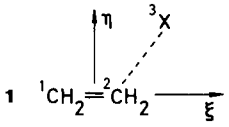
Simple Model for Radical Additions

By *Udo Höweler* and *Martin Klessinger**

Dedicated to Professor Wolfgang Lüttke on the occasion of his 65th birthday

Starting from a VB approach, we have recently developed a model for nonpolar radical reactions[1], which extends beyond the possibilities offered by known MO considerations[2] in that it permits estimation of the energies and geometries of the transition states as well as substituent effects. We demonstrate this here by describing the first applications of the model: intermolecular addition of a radical X to alkenes **1** and concerted [1,2]-migration in radicals.



The majority of reactions undergone by free radicals can be described by a three-center, three-electron system[1,3]; Figure 1 shows the characteristics of the potential surface for the ground-state reactions of such a system as a function of the position of center 3 in the ξ,η-plane, the separation of centers 1 and 2 being fixed; for a linear transition state the center 3 lies on the ξ-axis, and for a cyclic one, on the η-axis. The solid curve describes those geometries at which the 2,3-bond is formed and, hence, at which an activation barrier for intermolecular reactions occurs. The dotted curve designates the geometries at which the 1,2-bond is broken, so that reactions crossing this curve imply scission of this bond. The positions of both curves can be readily estimated qualitatively from

$$S_{12}^2 = \frac{1}{2}\left(\frac{m_{13}}{m_{12}} S_{13}^2 + \frac{m_{23}}{m_{12}} S_{23}^2\right) \quad (1a)$$

$$S_{23}^2 = \frac{1}{2}\left(\frac{m_{12}}{m_{23}} S_{12}^2 + \frac{m_{13}}{m_{23}} S_{13}^2\right) \quad (1b)$$

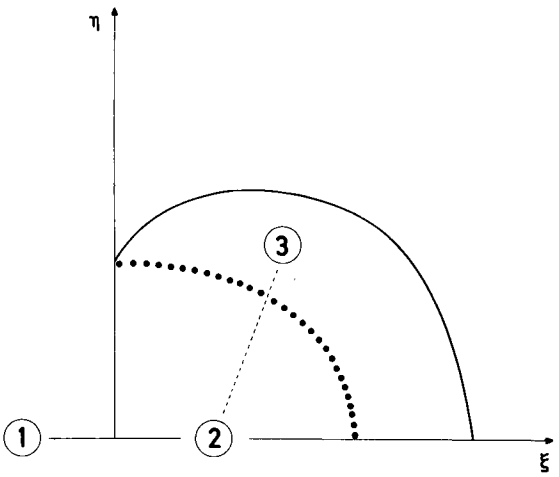


Fig. 1. Characteristics of the potential surfaces of the three-center, three-electron system (cf. text); geometries from equation (1a) (· · · ·) and equation (1b) (——) correspond to scission of the 1,2-bond and formation of the 2,3-bond, respectively.

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and the height $E_a - |\varepsilon_\infty|$ of the activation barrier relative to the energy $|\varepsilon_\infty|$ of the separated centers is given by

$$E_a = |\varepsilon_\infty| - m_{12}\left(S_{12}^2 + \frac{m_{13}}{m_{12}} S_{13}^2\right) \quad (2)$$

If both the overlap integrals $S_{\mu\nu}$ and the one-center energies h_ρ necessary for calculation of the parameter

$$m_{\mu\nu} = 1.75(h_\mu + h_\nu) + h_\kappa$$

are also known, the positions of the curves can be estimated quantitatively, thus forming the basis for a straightforward and illustrative discussion of free radical reactions.

By this means the following generalizations about the course of addition of a radical X to an alkene can be deduced from Figure 1 and from the dependence of the overlap integral $S_{\mu\nu}$ on the nuclear distance $R_{\mu\nu}$ and on the atomic number of the radical center:

- Thermal addition reactions proceed preferentially via linear transition states.
- In the linear transition state the length of the educt bond is almost unchanged. A shorter bond would lead to a "tighter" transition state.
- Cyclic transition states are unfavorable in reactions from the ground state and are only favorable if the bonds are lengthened.
- Within a given period the transition state becomes tighter as the atomic number of the radical center increases.
- Stabilizing substituents at the radical center, e.g. alkyl and aryl moieties, promote the reaction.

The effect of substituents on the radical center X was estimated as follows: If the one-center energies of the C atoms and of the radical center X are designated by h and $h_X = h + \Delta h$, respectively, then $m_{13}/m_{23} = 1$ and $m_{12}/m_{23} < 1$ or $m_{12}/m_{23} > 1$, depending on whether $\Delta h < 0$ or $\Delta h > 0$. Stabilization of the radical center ($\Delta h < 0$, $m_{12}/m_{23} < 1$) leads to a shift of the energy barrier to greater distances (cf. Fig. 2a) and to a smaller activation energy, whereas for the destabilization ($\Delta h > 0$, $m_{12}/m_{23} > 1$) the reverse behavior is expected (cf. Fig. 2b).

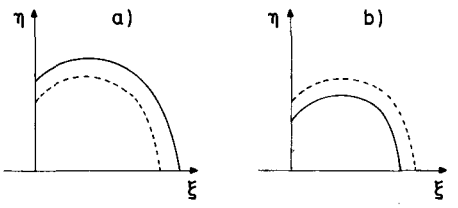

Fig. 2. Position of the activation barrier as a function of the one-center energies of the radical center: a) $\Delta h < 0$; b) $\Delta h > 0$. (The broken curve corresponds to $\Delta h = 0$.)

Table 1 summarizes the geometries (calculated using standard STO exponents for determination of the overlap integrals and EHT valence state ionization potentials for the one-center energies h_ρ[5] in determining the parameters $m_{\mu\nu}$ in eq. (1b)) of some transition states for the approach of the radical X along the direction of the newly formed bond (linear) and towards the middle of the original bond (perpendicular). The opening up of the transition state geometries due to stabilization of the radical center (for all X, $\Delta h \leq 0$) is indicated by the values in parentheses, which were obtained by neglecting the differences in the one-center energies ($\Delta h = 0$, $m_{12}/m_{23} = 1$).

Table 1. Distance R_{CX} [pm] in the transition state for the radical addition of X to ethylene for various 1,2-bond lengths R_{CC} (values in parenthesis refer to $m_{12}/m_{23} = 1$).

X	$\frac{m_{12}}{m_{23}}$	Linear		Perpendicular	
		$R_{CC} = 130$ pm	$R_{CC} = 150$ pm	$R_{CC} = 130$ pm	$R_{CC} = 150$ pm
H	0.97	190	210(210)	145	175 (170)
C	1.00	210	230(230)	[a]	190 (190)
N	0.96	200	220(220)	[a]	175 (165)
O	0.92	190	210(220)	[a]	160 (— [a])
F	0.89	175	195(190)	[a]	140 (— [a])
Cl	0.95	230	250(250)	165	210 (200)

[a] Condition (1a, b) not fulfilled.

The general course of the reaction and the structure of the quantum chemically calculated transition states in Table 2 are in excellent agreement with our results. The angle of approach is greater than 90° in all cases and the original bond is almost unchanged. The greatest deviation occurs with the fluorine atom, from which it can be concluded that the effect of the one-center energies (Δh) is not sufficiently reflected in this model derived for nonpolar reactions.

Table 2. Transition states for radical addition reactions to ethylene and acetylene.

X		R_{CC} [pm]	α [°]	R_{CX} [pm]	Ref.
H	C=C	136	106	203	[4a]
CH_3	C=C	132	109	230	[4b]
NH_2	C=C	148	>90	198	[4c]
F	C=C	—	>90	210	[4d]
H	C≡C	122	110	193	[4e]

Intramolecular reactions such as concerted [1,2]-migrations in radicals proceed along the energy valley between the two curves in Figure 1 and, hence, require lengthening of the 1,2-bond before the cyclic transition state is reached. The data in Table 1, in fact, show that for the simple model an activation barrier at $R_{12} = 130$ pm is found only for X = H and Cl, but at $R_{12} = 150$ pm a barrier and hence a cyclic transition-state is found for all X. This result is consistent with the transition-state geometries calculated by *Fossey* et al.[6].

The model we have developed therefore correctly treats those parameters which are decisive for estimating both the transition-state geometries and the activation energies of radical reactions and is comprehensive enough to be generally applicable.

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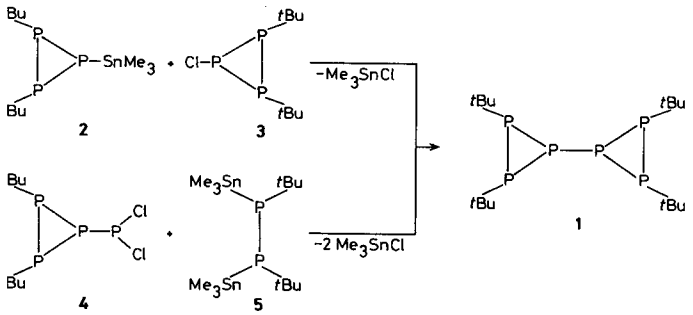
[6] J. Fossey, J.-Y. Nedelec, *Tetrahedron 37* (1981) 2967; for the concerted 1,2-migration in $H_2\overset{\oplus}{C}CH_2X$ systems, $R_{CC} = 150$ pm and $R_{CX} = 104$, 148, 173, 152, and 163 pm, respectively, were taken for X = H, CH_3, NH_2, OH, and F.

P_6tBu_4—The First 1,1'-Bicyclotriphosphane**

By *Marianne Baudler** and *Bernd Makowka*

Dedicated to Professor Kurt Issleib on the occasion of his 65th birthday

Triorganocyclotriphosphanes $(PR)_3$ are well-known compounds[1]. However, the synthetic potential of phosphorus three-membered ring compounds has scarcely been exploited. Starting from functionalized cyclotriphosphanes of the type $(PR)_2PX$ (X = functional group), we have now succeeded in linking two P_3 ring skeletons via a σ-bond.



2,2',3,3'-Tetra-*tert*-butyl-1,1'-bicyclotriphosphane **1** is obtained by reaction of 1,2-di-*tert*-butyl-3-trimethylstannylcyclotriphosphane **2**[2] with 1,2-di-*tert*-butyl-3-chlorocyclotriphosphane **3**[2] or by [1+2]-cyclocondensation of 1,2-di-*tert*-butyl-3-(dichlorophosphino)cyclotriphosphane **4**[2] with 1,2-di-*tert*-butyl-1,2-bis(trimethylstannyl)diphosphane **5**[2]. In contrast, demetalation of 1-potassium-2,3-di-*tert*-butylcyclotriphosphide[3] with iodine, 1,2-dihaloalkanes, or *N*-haloamines affords preferentially $(PtBu)_4$[4] and also other *tert*-butylphosphanes.

The pure, isolable **1**[5] is a colorless, crystalline solid (m.p. = 122—124°C, decomp. sealed tube), which is stable under an inert gas atmosphere. It is readily soluble in tetrahydrofuran (THF) as well as in aliphatic and aromatic hydrocarbons, but only moderately soluble in methanol. The compound, which in the solid state is only slightly sensitive to atmospheric oxygen, is rapidly oxidized in solution. Its composition is corroborated by the results of elemental analysis and by the mass spectrum [12 eV, 40°C, *m/z* 414, ($M^{\oplus}$, 8%), 357 ($M^{\oplus} - C_4H_9$, 100%)]. The IR and Raman spectra show bands in the P—P stretching- and deformation-regions[6]. The constitution of **1** follows from the NMR data (Table 1), in particular from a complete analysis of its $^{31}P\{^1H\}$-NMR spectrum (Fig. 1).

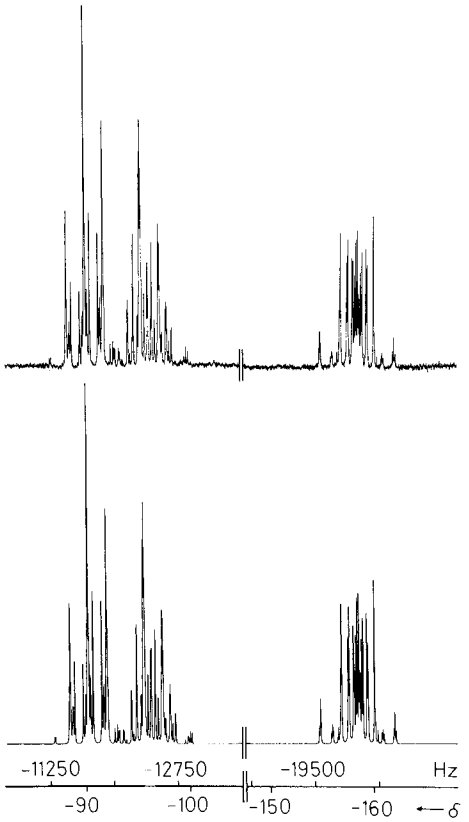
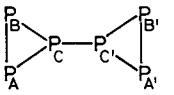


Fig. 1. Above: Observed 121.497 MHz $^{31}P\{^1H\}$-NMR spectrum of **1** in THF at 298 K. Below: Calculated spectrum of **1**.

Table 1. ^{31}P- [a], ^1H-, and ^{13}C-NMR data [b] of **1**.



	δ	J(PP) [Hz]	
^{31}P	−96.2 (P_A, $P_{A'}$)	−220.9 (P_AP_B, $P_{A'}P_{B'}$)	−171.6 (P_AP_C, $P_{A'}P_{C'}$)
	−90.2 (P_B, $P_{B'}$)	+164.6 ($P_AP_{C'}$, $P_{A'}P_C$)	−0.5 ($P_AP_{B'}$, $P_{A'}P_B$)
	−158.4 (P_C, $P_{C'}$)	+15.9 ($P_AP_{A'}$),	−233.8 (P_BP_C, $P_{B'}P_{C'}$)
		+9.8 ($P_BP_{C'}$, $P_{B'}P_C$)	+6.9 ($P_BP_{B'}$),
			−244.9 ($P_CP_{C'}$)
^1H [c]	+0.97 (P_AtBu)		
	+1.45 (P_BtBu)		
^{13}C [c]	+30.42 (P_AC)		
	+29.90 (P_ACC)		
	+34.24 (P_BC)		
	+33.23 (P_BCC)		

[a] THF, 298 K. [b] [D_6]Benzene, 299 K. [c] The assignment followed from selective decoupling experiments.

The chemical shifts of all P atoms lie in the high-field region characteristic for phosphorus three-membered ring compounds[1]. Whereas the positions of the signals of the *tert*-butyl substituted atoms are largely in accord with the mean of the $\delta(^{31}P)$ values of tri-*tert*-butylcyclotriphosphane ($\delta_{cis} = -71.0$, $\delta_{trans} = -109.6$[7]), those of the P atoms connected only to other phosphorus atoms are shifted strongly to high field. This may be attributable to a contraction of the exocyclic bond angles[8] upon substituting a *tert*-butyl group in $(PtBu)_3$ by a "P side-chain", which is also observed in similar compounds $[(PtBu)_2P-P(tBu)Cl$:

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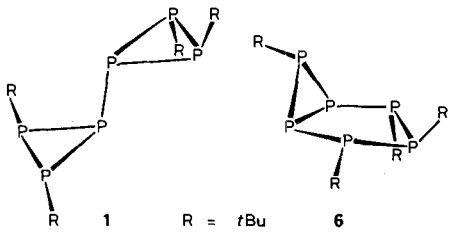
$\delta = -157.6$[2]; $(PtBu)_2P-P(cyclo\text{-}C_6H_{12})_2$: $\delta = -159.4$[9]]. Proof of the structure is furthermore provided by the large positive coupling constant $^2J(P_AP_{C'}) = {}^2J(P_{A'}P_C)$, which indicates approach of the lone-pairs of electrons on the P atoms involved[10].

According to the IR and Raman spectra (non-fulfillment of the alternative rule)[6] as well as to the order of magnitude of the $^3J_{PP}$ coupling constants [$^3J(P_AP_{A'}) > {}^3J(P_BP_{B'})$][10], of the two possible configurational isomers, which differ from each other in the relative arrangement of the *trans*-oriented *tert*-butyl groups at the two three-membered rings, the sterically more favorable all-*trans*-isomer (C_2 symmetry) is present as an enantiomeric pair.



1 R = *t*Bu 6

The 1,1'-bicyclotriphosphane **1** is a constitutional isomer of the bicyclo[3.1.0]hexaphosphane **6**, formed by dehalogenation of a mixture of $tBuPCl_2$ and PCl_3 with magnesium[10c]. Thermolysis of **1** (128 °C) leads not only to disproportionation into $PtBu_3$, P_8tBu_6[11], and *tert*-butylphosphanes richer in P, but also, on a limited scale, to isomerization to **6**.

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[5] Procedure: **1**: A solution of **3** (2.9 g, 12.0 mmol) in 20 mL THF is added dropwise over a few minutes to a stirred solution of **2** (4.5 g, 12.1 mmol) in 50 mL THF at −40 °C under an inert gas atmosphere. The mixture is then stirred for 1 h at −40 °C and subsequently for 2 h at room temperature, the solvent removed under reduced pressure, and the trimethylstannyl chloride condensed via a bent tube (bath temperature: 40–45 °C; cold trap: −196 °C; pressure: 0.1 torr; duration: 4 h). Dissolving the solid yellow residue with vigorous stirring in 150 mL methanol (40 °C) and subsequent cooling to −78 °C (12 h) affords a pale-yellow solid, which is separated in the cold and successively recrystallized from THF/methanol (1 : 1) and THF (in each case dissolving at room temperature, crystallization at −35 °C); yield 1.3 g (26%) colorless **1**.
[6] IR (<600 cm^{-1}, KI pellet): 570 (m), 523 (w, sh), 482 (m), 444 (m), 425 (w, sh), 391 (m), 359 (m), 349 (m) cm^{-1}; Raman (<600 cm^{-1}, krypton): 580 (m), 572 (m), 532 (s), 470 (vw), 451 (m), 421 (m), 390 (m), 363 (vw), 340 (m), 259 (m), 245 (m), 189 (s), 147 (s) cm^{-1}.
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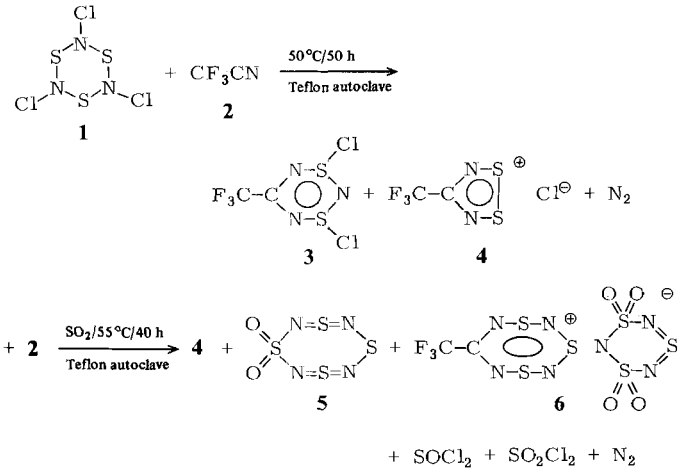
Synthesis and Structure of the 7-Trifluoromethyl-1,3,5,2,4,6,8-trithiatetrazocine Cation**

By *Hans-Ulrich Höfs, Gabriele Hartmann, Rüdiger Mews**, and *George M. Sheldrick*

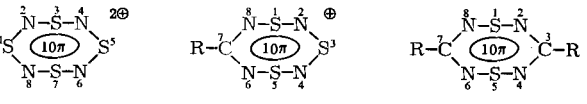
Dedicated to Professor Wolfgang Lüttke on the occasion of this 65th birthday

The reactions of 1,3,5-trichloro-1,3,5,2,4,6-trithiatriazine **1** with trifluoroacetonitrile are very complex; depending on the reaction conditions, the solvent, and the material of the reaction vessel[1], different products can be obtained. On carrying out the reaction in the absence of solvent, the dithiatriazine **3** (21%)[2] and the dithiadiazolylium chloride **4** (45%)[3] are obtained; when SO_2 is used as solvent, it enters into the reaction: In addition to **4**, the *S,S*-dioxide **5** is formed, along with about 4% of the salt **6**[5], which contains the cyclic, eight-membered 7-trifluoromethyl-1,3,5,2,4,6,8-trithiatetrazocine cation and the well known 1,1,3,3-tetraoxo-1,3,5,2,4,6-trithiatriazine anion[6,7]. **5** is accessible via an alternative route[4].



+ $SOCl_2$ + SO_2Cl_2 + N_2

The cation in **6** is the missing link in the series of isoelectronic heterocycles $S_4N_4^{2\oplus}$ **7**[8] $RCS_3N_4^{\oplus}$, and 3,7-$(RC)_2S_2N_4$ **8**[9–11], which have attracted increasing interest in recent years, both preparatively[9,10] as well as theoretically[9–11]. Systems such as these are especially suitable for checking the general applicability of theoretical models developed for organic compounds.



7 8

The "electron-rich" 10π-dication $S_4N_4^{2\oplus}$ **7**, which can be prepared by oxidation of the 12π S_4N_4-cage, is (as expected according to the Hückel rule) planar and exhibits almost equal SN distances (mean length 155.2 pm). Formal replacement of "$S^{\oplus}$" in the 1,5-position by the isolobal sp^2 carbon should lead to very little change in the electronic

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structure of the ring system. Model calculations on **8** show[10] that this 10π ring system, with alkyl and aryl substituents, has a planar monocyclic structure; π-donor ligands can induce a pseudo-Jahn-Teller distortion, which leads to a bicyclic 8π system with *trans*-annular S–S bonding[10, 14]. The cation is therefore expected to have a planar structure; this has been confirmed by an X-ray structure analysis of **6** (Fig. 1)[12]. C1,S5 and S3,S7 respectively lie

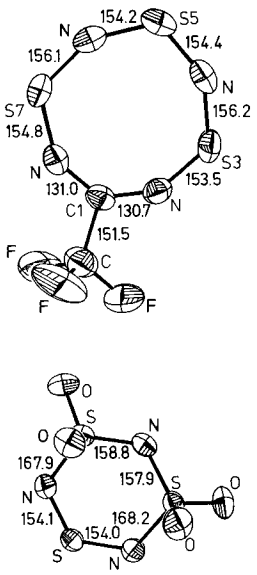

Fig. 1. The structure of **6** in the crystal [12], with bond lengths [pm]. The mean S–O distance is 143.0 pm.

only slightly above and slightly below the plane through the four N atoms (6.2, 7.2, −7.7, −9.0 pm); this slight folding of S3/S7 does not, however, lead to any *trans*-annular S–S interaction (S–S 400.8 pm). The S–N distances (mean value 154.9 pm) are almost identical; they alternate very little more than in the $S_4N_4^{2\oplus}$ ion. In both systems the average S–N bond lengths are very nearly equal and are about 1.5 pm shorter than in the neutral aryl derivatives of **8**[9]; a similar shortening is observed for the C–N bonds. The anion $S_3N_3O_4^{\ominus}$ has almost the same geometry as has been found in $S_5N_5^{\oplus}S_3N_3O_4^{\ominus}$[7] and $(S_3N_2^{\oplus})_2(S_3N_3O_4^{\ominus})_2$[6].

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1,2,4,6-Tetraphenylphosphininium Tetrachloroaluminate, the First Phosphininium Salt Analogous to the Pyridinium Salts**

By *Trupti N. Dave, Hans Kaletsch,* and *Karl Dimroth**

Dedicated to Professor Kurt Issleib on the occasion of his 65th birthday

Whereas pyridine and its derivatives are readily alkylated or protonated to pyridinium salts, all attempts to prepare phosphininium salts from phosphinines in an analogous way have so far failed. Presumably the reason for this is the opposite distribution of electrons in the two ring systems. The electropositive phosphorus atom lowers the nucleophilicity of the phosphinine[1a], and the larger C(ring)–P–C(ring) angle increases the s-character of the lone pair of electrons. Hence, any bonding to an electrophile requires additional energy because of the rehybridization associated with a change in geometry of the ring system[1b]. Phosphininium ions bearing three organic groups on the phosphorus have been postulated as intermediates in some reactions of phosphinines[2], but no salt of such a cation has thus far been obtained. All the previously reported salts containing phosphorus cations of coordination 3 have at least one substituent bearing a lone pair of electrons, e.g. a dialkylamino-[3] or a pentamethyl-2,4-cyclopentadienyl group[4]. In both these cases it is assumed that the n-electrons of the neighboring atom or the

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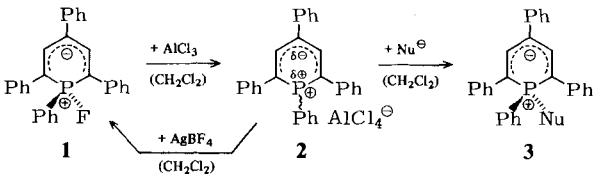
π-electrons, as in the case of the cyclopentadienyl moiety, contribute to stabilization of the cation by satisfying the electron deficit on the phosphorus.

Herein, we describe the first synthesis of a stable, crystalline phosphininium salt with three carbon residues bonded to the phosphorus, namely the 1,2,4,6-tetraphenylphosphininium tetrachloroaluminate **2**. As starting material we used 1-fluoro-1,2,4,6-tetraphenyl-λ^5-phosphinine **1**. **2** was obtained on treatment of **1** (m.p. 155–156 °C, 51% yield, prepared by reaction of 2,4,6-triphenylphosphinine with phenyldiazonium tetrafluoroborate, in analogy to the procedure described in ref. [5]) with 1.5 mol of freshly sublimed aluminum chloride per mol **1** in dichloromethane at −78 °C under argon. The yellow crystals of **2** precipitated on stirring and slowly heating the solution to room temperature. According to elemental analysis the crystals contain 0.5 mol CH_2Cl_2.



In the ^{31}P-NMR spectrum the $^1J_{PF}$ coupling of **1** (1116 Hz) disappears completely during the reaction. The ^{31}P resonance at $\delta = 27$ in the ^{1}H-decoupled spectrum of **1** is transformed into a sharp signal at $\delta = 103$. In the case of **2** the NMR signals of the ring protons (**1**: $\delta = 7.9$, 2H, dd, $^4J_{HF} = 6$ Hz, $^3J_{HP} = 38$ Hz) lie at $\delta = 8.28$ (2H, d, $^3J_{HP} = 33.9$ Hz). A ^{13}C-NMR low-temperature spectrum of **2** could not be recorded because of the poor solubility and high sensitivity of **2**; however, the $AlCl_4^⊖$ formed by halogen exchange was easily recognizable by its intense ^{27}Al-NMR signal at $\delta = 103$[6]. As expected the MS/FD spectrum did not contain a peak at $m/z = 401$ for the non-volatile cation **2**. Peaks were observed, however, for the radical cation of 2,4,6-triphenylphosphinine ($m/z = 324$ (48%)) and the radical cations of the OH- and the Cl-addition products ($m/z = 418$ (42%) and 436 (100%), respectively), which are formed during the recording of the spectrum.

2 reacts immediately and quantitatively with nucleophiles such as methanol, ethanol, phenyllithium or chloride ions to give the known λ^5-phosphinine derivatives **3** (Nu = OMe, OEt, Ph[7], Cl), of which the latter loses chlorobenzene (detected gas-chromatographically) with formation of 2,4,6-triphenylphosphinine on gently warming. With water, **2** forms 1-hydroxy-1,2,4,6-tetraphenylphosphinine, which rearranges via a known route into 1-oxo-1,2,4,6-tetraphenyl-1,2-dihydrophosphinine. Addition of $AgBF_4$ to **2** in CH_2Cl_2 gives **1** in quantitative yield. This confirms the strong electrophilicity of the phosphorus in **2**, which must be far greater than that of the boron in BF_3 (see also [5]).

1-Chloro-1,2,4,6-tetraphenyl-λ^5-phosphinine (**1**, Cl instead of F) is unstable. Reaction of 1,1-dichloro-2,4,6-triphenylphosphinine with aluminum chloride or antimony pentachloride in dichloromethane leads to formation of sparingly soluble 1-chloro-2,4,6-triphenylphosphininium salts of type **2** (^{31}P-NMR: $\delta = +96.9$ and $+96.2$, respectively) which, however, could not be isolated completely pure.

The formula of **2**, which would indicate very little, if any, flow of electrons from the 6π-system of the five C-atoms to the $P^⊕$-center, is consistent with its unusual electrophilicity, even towards $BF_4^⊖$. Conclusive statements about the ground state, however, cannot be made until a complete evaluation of the X-ray structure analysis of **2**[8] and measurement of ^{13}C-NMR spectra of similar phosphininium salts have been carried out.

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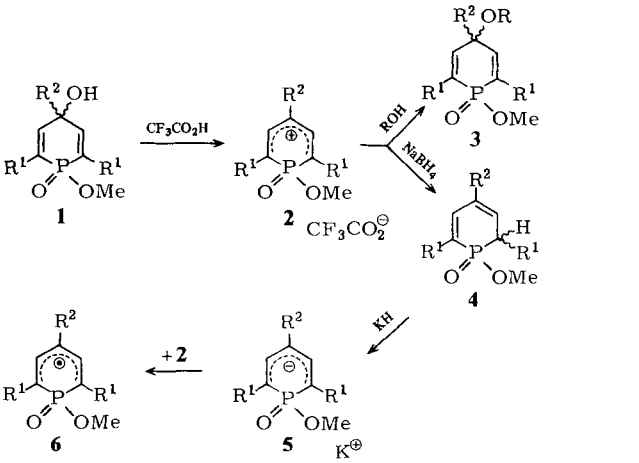
Delocalized Carbocations, Carbanions and Radicals of 2,4,6-Substituted 1-Methoxy-1-oxo-λ^5-phosphinines**

By *Karl Dimroth**, *Hans Kaletsch*, and *Trupti N. Dave*

Triphenylphosphonium salts, phosphonates and phosphinates, as well as well as phosphane oxides with an α-CH group are readily deprotonated to stable carbanions. Their reactions with various types of electrophiles are among the most important ones in preparative organic chemistry[1]. According to *Creary* et al.[2], phosphonates which contain a mesyloxy group on a secondary or tertiary α-C atom react with nucleophiles. In such reactions, destabilized carbocations[3] must be assumed as intermediates.

Some years ago we obtained the salt **2a**, containing a deep-blue, stable, delocalized carbocation, on reaction of



a, $R^1 = R^2 = Ph$; **b**, $R^1 = R^2 = C_6H_4OMe(4)$
c, $R^1 = Ph$, $R^2 = C_6H_4OMe(4)$; **d**, $R^1 = tBu$, $R^2 = C_6H_4OMe(4)$

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both the pure *E*- as well as the pure *Z*-isomer of the cyclic phosphinate **1a** with trifluoroacetate acid[4]. **2a** adds nucleophiles such as water, methanol or ethanol at C-4 to give the *E/Z*-mixture **3a** (R = H, Me, Et); hydride ions add at C-2 to give the *E/Z*-mixture **4a**.

The 5π delocalization, competing for the destabilization by the phosphinic acid group, accounts for the stability of the carbocation of **2**. The species **2b** is known[4a,b]. Recent, independent experiments[2,3] encouraged us to prepare the salts **2c** and **2d** (containing deep-blue and deep-red cations, respectively[6]) from **1c** and **1d** by reaction with trifluoroacetic acid or aluminum chloride in dichloromethane. **2c** and **2d** likewise add nucleophiles such as water, methanol or ethanol to give the *E/Z* mixture of **3c** and **3d**, respectively (R = H, Me, Et); hydride ions add to C-2 to give **4c** and **4d**, respectively. **4c** and **4d** react with potassium hydride in tetrahydrofuran (THF) to give the salts **5c** and **5d** containing stable delocalized anions. A mixture of equimolar amounts of **2c** and **2d** in dichloromethane and of **5c** and **5d**, respectively, in THF at room temperature, leads to formation of the radicals **6c** and **6d**, respectively, which are stable for days in the absence of air; their phosphorus coupling constants $a_p = 2.3$ mT compare very well with those of the well known radicals **6a** ($a_p = 2.31$ mT), and **6**, $R^1 = t\text{Bu}$, $R^2 = C_6H_3(t\text{Bu})_2(3,5)$ ($a_p = 2.35$ mT)[7]. Table 1 contains the relevant ^{1}H-, ^{13}C- and ^{31}P-NMR data of

Table 1. Most important NMR data of **1c**, **d**, **2c**, **d**, and **5c**, **d**. *J* in Hz. Standard: ^{1}H-NMR (TMS); ^{13}C-NMR (TMS); ^{31}P{^{1}H}-NMR: 85% H_3PO_4 ext.

Cpd.	^{1}H(Ring) δ (^3J(PH))	^{13}C-2/6 δ (^1J(PC))	^{13}C-3/5 δ (^2J(PC)) (^1J(CH))	^{13}C-4 δ (^3J(PC))	^{31}P δ
1c	6.65 [a] (34.7)	128.1 [d] (120.6)	149.1 (8.1) (160.3)	70.42 (17.7)	17.8 [a]
2c	8.48 [a] (39.1)	—	—	—	20 [a]
5c	7.55 [c] (31)	100.6 [c] (133.8)	136.7 (9.55) (146.3)	110.9	45.7 [c]
1d	6.33 [a] (35.4)	138.5 [b] (114.5)	147.8 (8.8) (158.2)	71.3 (21.3)	22.9 [a]
2d	8.2 [a] (40.8)	158.3 [a] (111)	137.6 (6.6) (162.5)	154.6 (26.5)	15.6 [a]
5d	7.24 [c] (33.8)	105.1 [c] (130.9)	135.0 (10.3) (142.2)	105.3 (15.5)	53.3 [c]

[a] In CD_2Cl_2. [b] In CD_3OD. [c] In [D_8]tetrahydrofuran. [d] In [D_6]dimethyl sulfoxide.

the most important compounds described here; in the case of **2c**, however, the assignment of the ^{13}C-NMR signals is not absolutely certain because of the many phenyl C-atoms. The salt **2c** is very easily accessible, if 1,1-dimethoxy-4-(4-methoxyphenyl)-2,6-diphenyl-λ^5-phosphinine[5] is first converted with $SOCl_2$ or PCl_5 in dichloromethane into the *E/Z*-4-chloroderivative **3c** (Cl instead of OR) and then allowed to react with aluminum chloride.

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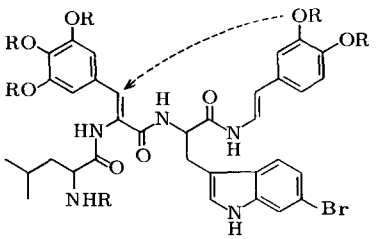
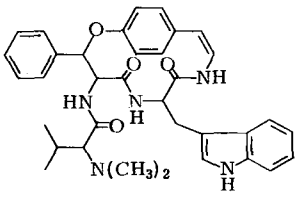
Total Synthesis of Hexaacetylcelenamide A**

By *Ulrich Schmidt** and *Jochen Wild*

Three types of cyclic peptide alkaloids containing 12-, 13-, and 14-membered ring systems have so far been isolated from plants[1]. Their occurrence is strictly confined to the Rhamnaceae and Sterculiaceae. The isolation of closely related linear compounds from pacific sponges—i.e. a completely different type of biological substrate—by *Andersen* et al.[2] was therefore very surprising. These linear peptide alkaloids—e.g., celenamide A **1a**, which were all isolated as peracetyl derivatives—formally derive from the peptide alkaloid derivatives, e.g. interregin **2**, by ring-opening with β-elimination (dotted arrow in **1**) and transformation into the *trans-N*-styrylamide. As extension to the total synthesis of 13- and 15-membered cyclic peptide alkaloids[3,4] and of dihydro derivatives of the 14-membered cyclic peptide alkaloids[5] we now describe the first total synthesis of a linear peptide alkaloid, the hexaacetylcelenamide A **1b**. Key reactions in the total synthesis are two condensation reactions with phosphonoglycine esters **3** and **9**[6] for the synthesis of dehydroamino acids and dehydropeptides.



1a, R = H
1b, R = $COCH_3$



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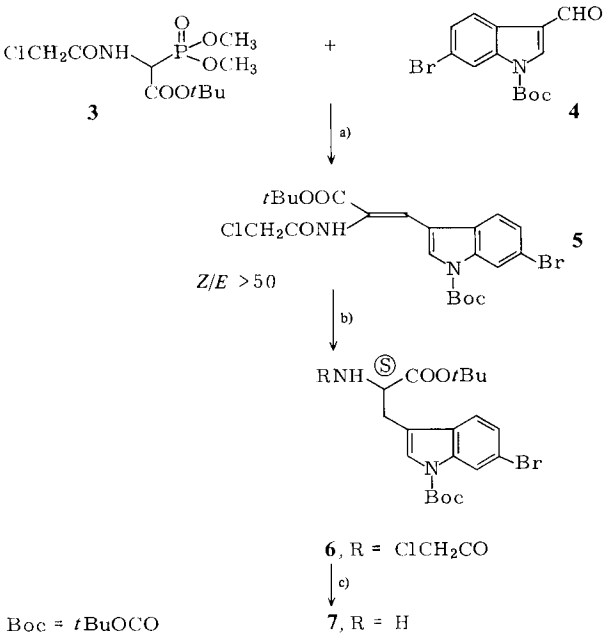
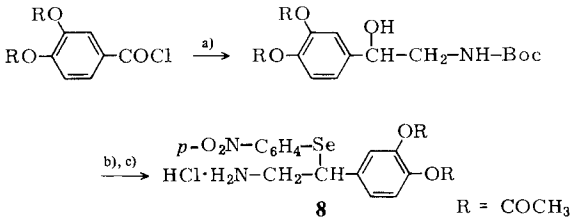
[**] Synthesis of Peptide Alkaloids, Part 10; Amino Acids and Peptides, Part 49. This work was supported by the Fonds der Chemischen Industrie, The Deutsche Forschungsgemeinschaft, and BASF AG. We thank Prof. Dr. *G. Jung* for determining the conformation of the leucine in the hydrolyzate and Prof. Dr. *J. Andersen* for supplying us with the original NMR and IR spectra of hexaacetylcelenamide A.—Part 9: [4]; Part 48: U. Schmidt, A. Lieberknecht, H. Griesser, H. Bökens, *Liebigs Ann. Chem.*, in press.

Like clionamide, which was likewise isolated from *Cliona celata*[7], celenamide also contains 6-bromotryptophan—apparently a characteristic amino acid for marine animals. In our synthesis of clionamide[8] we constructed this amino acid from 6-bromoindole and the oxime of ethyl bromopyruvate[9] and separated the *S*-compound from the racemate by cleavage with acylase. More convenient for this synthesis is the condensation of **3**[6] with **4**[10] to give the dehydroamino acid derivative **5**, whose enantioselective homogeneous hydrogenation with Monsanto catalyst[11] leads with high enantioselectivity (*ee* > 98%) to

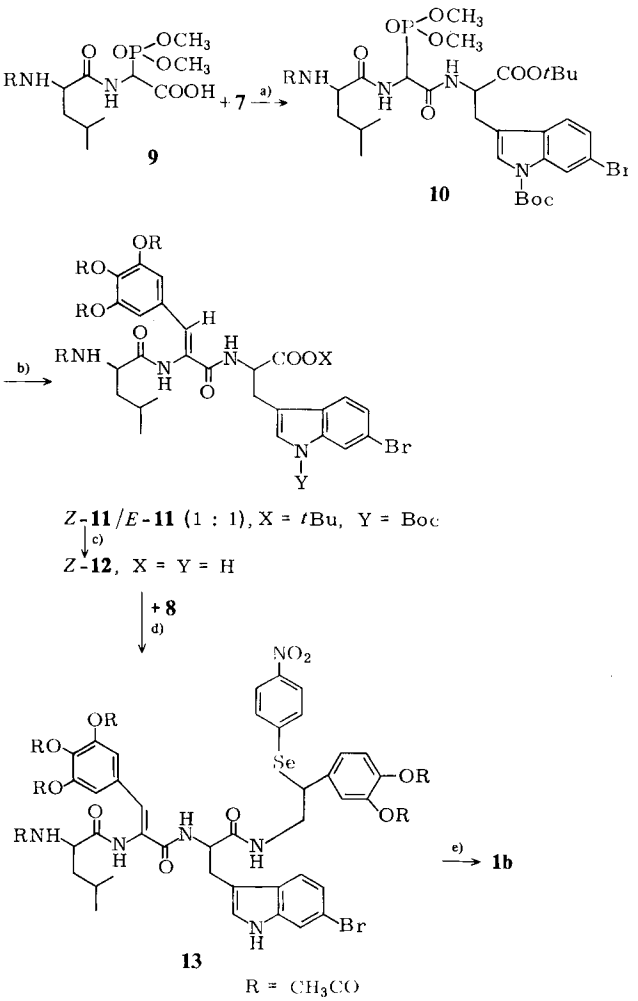


Scheme 1. Enantioselective synthesis of the (*S*)-6-bromotryptophan derivative **7**. a) KO*t*Bu/CH_2Cl_2/ −30°C. b) Monsanto catalyst ([Rh(1,5-cod)(*R,R*-dipamp)]$^{\oplus}BF_4^{\ominus}$)/H_2, EtOH (40°C, 18 h) (cod = 1,5-cyclooctadiene, dipamp = *P,P'*-ethylenebis[*o*-methoxyphenyl(phenyl)phosphane]. Enantiomeric excess: 98% *S*, determined by chromatography on a HPLC column with chiral stationary phase (BAKERBOND) (eluent mixture: 2-propanol/hexane 1 : 19) and the racemate as reference compound. c) *N*-piperidinethiocarbamide, EtOH (80°C).

the (*S*)-*N*-chloroacetyl-6-bromotryptophan **6**. The chloroacetyl group was cleaved with *N*-piperidinethiocarbamide[12] to give **7** (Scheme 1); **7** was then coupled with the (*S*)-leucyl derivative **9**[6] to give the phosphono-tripeptide **10**, which condensed directly with triacetoxybenzaldehyde to give the *E/Z* mixture of the two dehydropeptides *E*-**11**,*Z*-**11**. These isomers were separated by medium pressure chromatography and further worked up individually[13]. On removing the Boc protecting group, the *tert*-butyl ester was cleaved at the same time; *Z*-**12** was obtained. Amide formation using the selenium reagent **8** (Scheme 2) furnished the educt **13** for the oxidative elimination step to the hexaacetylcelenamide **1b** (Scheme 3). In the cleavage



Scheme 2. Synthesis of the selenium reagent **8**. a) Successive reaction with CH_2N_2; HCl; KI cat. + NaN_3; H_2/Pd + $(Boc)_2O$; $NaCNBH_3$; b) *p*-Nitrophenylselenium cyanide, tributylphosphane; c) HCl/dioxane, resorcin dimethyl ether.



Scheme 3. Total synthesis of hexaacetylcelenamide A **1b**. a) Dicyclohexylcarbodiimide (DCCD)/CH_3CN; b) Lithium diisopropylamide/tetrahydrofuran; 3,4,5-triacetoxybenzaldehyde; medium pressure chromatographic separation of the isomers; c) HCOOH/40°C; d) DCCD, hydroxysuccinimide, NEt_3, acetonitrile; e) $NaIO_4$/dioxane/water.

reaction, only the (*E*)-*N*-styrylamide was formed. The NMR and IR spectra of the synthetic and natural products were identical. The synthesis concomitantly proved the configuration of the double bond in the dehydroamino acid moiety.

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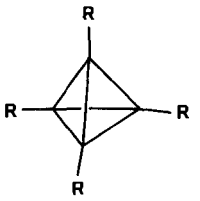
[13] The configuration at the double bond of dehydrotripeptide **11** could be determined by ^{1}H-NMR (300 MHz) spectroscopy. Chemical shift of the α-hydrogen atoms of the terminal amino acids: *Z*-**11**: CH-Leu $\delta = 4.42-4.46$, CH-Trp $\delta = 4.85$ (dd, $J = 15$ Hz, $J' = 5.4$ Hz); *E*-**11**: CH-Leu $\delta = 4.50-4.59$, CH-Trp $\delta = 4.50-4.59$.

Tetra-*tert*-butyltetrahedrane—Crystal and Molecular Structure**

By *Hermann Irngartinger**, *Annette Goldmann*, *Reiner Jahn*, *Matthias Nixdorf*, *Hans Rodewald*, *Günther Maier*, *Klaus-Dieter Malsch*, and *Rolf Emrich*

So far tetra-*tert*-butyltetrahedrane **1** is the only isolated and unequivocally identified tetrahedrane derivative[1]; however, although its spectroscopic properties have been intensively investigated[2,9], an X-ray structure analysis, which we report here, was missing. At room temperature under various conditions, **1** crystallizes only in a trigonal-rhombohedral modification[3], which affords insufficient reflections in the high-angle region as a result of disorder. Despite measurements between -160 °C and room temperature, no real improvements could be achieved. At -60 °C however a hexagonal modification[3] with a higher order could be grown.



1, R = *t*Bu
2, R = Me
3, R = H

In the hexagonal modification the tetrahedrane molecules **1** lie on a crystallographic mirror plane (Fig. 1); however the atomic coordinates exhibit only slight deviations from the highest possible molecular T_d symmetry. All the groups have a staggered conformation (Fig. 1). Nevertheless, force field[4a,c] and MNDO calculations[4b] indicate that the isolated molecule should deviate from this symmetry. Accordingly, because of mutual repulsion, all the *tert*-butyl groups should be twisted by 10.5—14°[4] in the same direction out of an arrangement with mirror symmetry, resulting in chiral T symmetry for the isolated molecule. Because of mirror symmetry in the crystal, such an arrangement is not possible in space group $P6_3/m$[3]. Nevertheless a disordered, chiral conformation can be derived from the magnitude and direction of the thermal vibration parameters of the atoms of **1**.

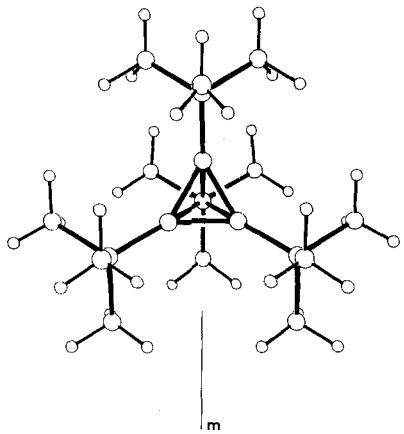


Fig. 1. Projection of the structure of **1** onto a tetrahedral plane (with crystallographic mirror plane).

Whereas the vibrations of the atoms of the tetrahedron and of the quaternary C atoms are small and almost isotropic, those of the carbon atoms of the methyl groups are relatively large and very much anisotropic (Fig. 2). Analysis of the vibration parameters using the method of rigid body motion[5] affords intramolecular torsional vibrations (9—15°) for individual *tert*-butyl groups around the C—C bonds linking these groups to the tetrahedron. Vibration parameters of this type can be produced by real torsional vibrations in a molecule of T or T_d symmetry or be caused by torsional disorder of the *tert*-butyl groups with the same occupancy at both terminal points of the vibrational amplitudes. In this way, two enantiomeric molecules of chiral T symmetry can be disordered at both sides of the mirror plane (enantiomeric disorder). The values measured for the central region of the tetrahedron are only slightly influenced by these effects.

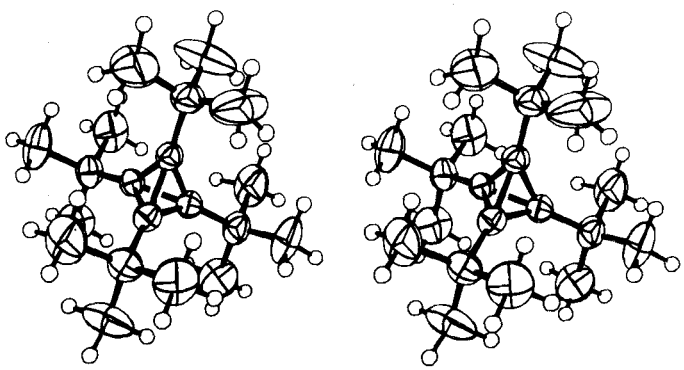


Fig. 2. Stereoscopic view of **1** with the ellipsoids of thermal vibration for the C-atoms (50% probability).

Compared with normal C—C single bonds (1.54 Å), the C_R—C_R bond lengths in the tetrahedron (average value 1.485 Å, Fig. 3) are relatively short due to the considerable steric strain in this system and the bending of these bonds. The tetrahedrane system cannot be regarded as a bicyclo[1.1.0]butane with a zero bridge in the 2,4-positions, since a shorter bond length would be expected with an interplanar angle of 70.5° between the three-membered

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rings[6]. Semiempirical calculations gave larger, and ab initio methods (for the unsubstituted tetrahedrane **3**) smaller values for the C_R-C_R bond (Table 1). Compared with $C(sp^3)-C(sp^3)$ single bonds (1.54 Å), the C_R-C_Q bonds (1.490, corrected[7] 1.502 Å) are short, but they have the

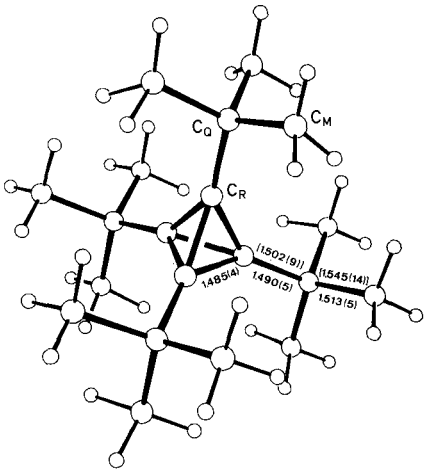

Fig. 3. Structures of **1** with averaged bond lengths [Å] (in round brackets: values of scatter; in square brackets: corrected values [7]). Individual values [Å] (in round brackets: standard deviations; in square brackets: corrected values [7]); C_R-C_R: 1.487(5), 1.487(3), 1.480(3), 1.487(5); C_R-C_Q: 1.503(4) [1.512], 1.480(7) [1.499], 1.486(4) [1.495]; C_Q-C_M: 1.477(5) [1.531]—1.539(4) [1.561]. The C–C–C bond angles at the tetrahedron are consistent with the 60.0° and 144.7° angles of a regular tetrahedron, as is the interplanar angle of 70.5° between the planes of the three-membered rings.

Table 1. Comparison of the experimental (**1**) and calculated (**1**—**3**) bond lengths [Å].

	1 Exp. [a]	[Corr.] [a]	**1** Force field [b]	**1** MNDO [c]	**2** MNDO [d]
C_R-C_R	1.485		(1.482)	1.534	1.524
C_R-C_Q	1.490	[1.502]	1.487—1.532	1.501	—
C_Q-C_M	1.513	[1.545]	—	1.559	—
3:	IMOA [e]	4-31G [f]	STO-3G [g]	CEPA [h]	
C_R-C_R	1.491	1.482	1.473	1.470	

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same order of magnitude as the $C(sp)-C(sp^3)$ single bonds in *tert*-butylacetylene (1.498 Å from electron diffraction measurements[8]). According to ^{13}C-NMR measurements, the orbitals of the tetrahedrane atoms in these bonds are, in fact, sp-hybridized[9]. Because of torsional vibration or disorder the C_Q-C_M bonds (average length 1.513 Å) appear shortened; however after correction for thermal motion the value of 1.545 Å[7] is within the normal order of magnitude.

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1, 66809-06-1

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[11] Further details of the crystal structure investigation can be obtained from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD 50989, the names of the authors, and the journal citation.

Cations of Boron with Coordination Number Three: 1,3,2,4-Diazadiboretidinium Salts

By *Heinrich Nöth** and *Siegfried Weber*

The readily accessible *tert*-butylimino-(2,2,6,6-tetramethylpiperidino)borane **1** is haloborated by boron halides; for example BBr_3 yields the four-membered heterocycle **2**[1]. Addition of dibromo(methyl)borane to **1** leads, via methyloboration[2], to the heterocycle **3**, whose structure can be unequivocally derived from the NMR data. In contrast, **1** undergoes a phenyloboration with dichloro(phenyl)borane to give **4** and a chloroboration to afford **5**. We have not yet succeeded in separating these isomers.

Unexpectedly, addition of bromodimethylborane to **1** affords a 1:1 adduct, whose ^{11}B-NMR spectrum exhibits only one signal at $\delta=48.9$; furthermore, only one ^{1}H- and ^{13}C-NMR signal is observed for the B-methyl and the methyl groups on the piperidine ring. These data indicate a higher symmetry for the adduct than, e.g., in **2**. A considerable electrical conductivity in CH_2Cl_2 solution and the

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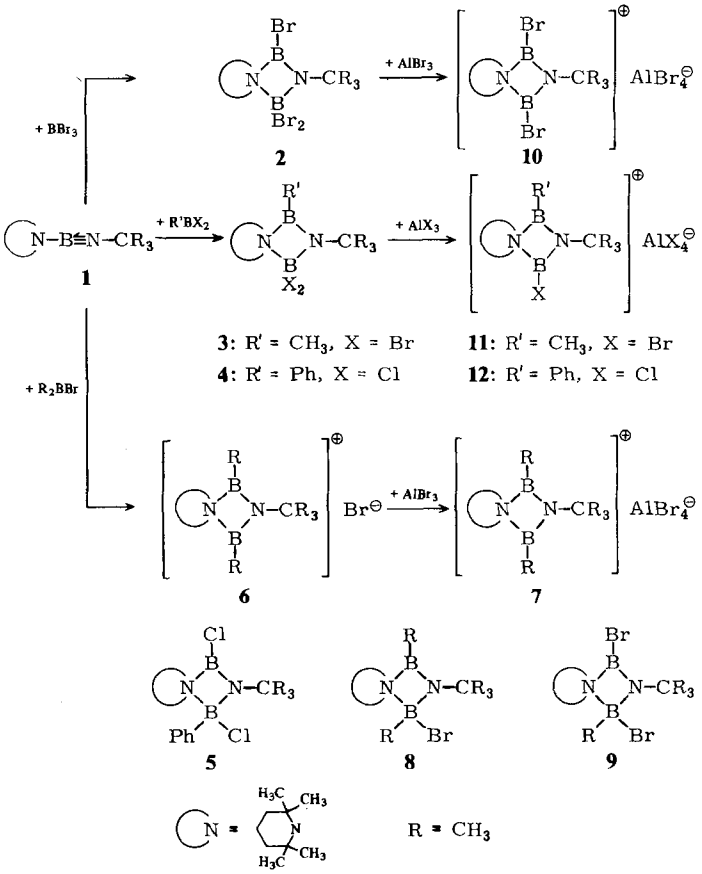
spectroscopic data suggest the spirocyclic 1,3,2,4-diazadiboretidinium bromide **6**. This assignment is corroborated by the addition of $AlBr_3$: The ^1H-, ^{13}C-, and ^{11}B-NMR parameters of **6** hardly change, since the Lewis acid $AlBr_3$ only converts the bromide **6** into the tetrabromoaluminate **7**.



These results indicate that the expected adduct **8** is unstable because of the insufficient acidity of the CH_3BN_2 moiety, and at the same time explains the fact that **1** undergoes methyl- and not bromoboration with CH_3BBr_2[2]: The product of bromoboration, **9**, is formed first, and then rapidly rearranges to the more stable **3** via bromide migration.

The high mobility of the halides in **2**, **3**, **4**, and **5** at the tetracoordinated boron atom is also underlined by the fact that aluminum halides abstract a halide ion from the heterocycles, forming the tetrahalogenoaluminates **10**, **11**, and **12**; as expected, the isomeric mixture **4**, **5** leads to the same cation. Characteristic data are shown in Table 1.

The novel cations **6**, **7**, **10**, **11**, and **12**, in which boron has the coordination number 3, contain a diborylamine structural element ($>B-\ddot{N}-B<$); this is isoelectronic with allyl cations, and we regard this as the reason for their high tendency of formation.

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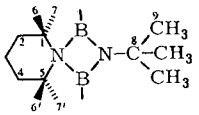
Table 1. Some characteristic NMR data for compounds **3**—**7** and **10**—**12**. The compounds **2**—**6** were obtained from equimolar amounts of **1** and halogen(organo)boron in pentane, and the tetrahalogenoaluminates, from these compounds and the equivalent amount of AlX_3 in CH_2Cl_2 solution [3].



3: M.p. = 99—100 °C; $\delta^{11}B$ 38.1, 0.0; δ^1H 1.38—0.95 (H2—4), 1.71 (H7), 1.65 (H6), 1.47 (H9), 0.52 (BCH_3)

4: $\delta^{11}B$ 36.8, 9.6; $\delta^{13}C$ 62.4 (C1,5), 53.3 (C8), 40.6 (C2,4), 34.2, 32.0, 27.6, 27.4 (C6,7), 30.7 (C9), 16.5 (C3) as well as signals in the phenyl group region

5: $\delta^{11}B$ 29.0, 21.9; $\delta^{13}C$ 59.9 (C1,5), 53.8 (C8), 39.9 (C2,4), 32.5, 27.8 (C6,7), 31.2 (C9), 16.3 (C3) as well as signals in the phenyl group region

6: M.p. = 108—110 °C (decomp.); $\delta^{11}B$ 48.9; δ^1H 1.86 (H2—4), 1.53 (H6,7), 1.49 (H9), 1.37 (BCH_3); $\delta^{13}C$ 5.7 (BCH_3) and further signals

7: M.p. = 151—152 °C (decomp.); $\delta^{11}B$ 47.8; $\delta^{27}Al$ 79.9, $h_{(1/2)}$ 15 Hz; δ^1H 1.83 (H2—4), 1.48 (H6,7), 1.41 (H9), 1.30 (BCH_3)

10: Decomp. 74—76 °C; $\delta^{11}B$ 36.8; $\delta^{27}Al$ 79.7, $h_{(1/2)}$ 15 Hz; δ^1H 2.02 (H2—4), 1.70 (H6,7), 1.58 (H9)

11: Decomp. 117—118 °C; $\delta^{11}B$ 47.8, 36.5; $\delta^{27}Al$ 79.9, $h_{(1/2)}$ 15 Hz; δ^1H 1.92 (H2—4), 1.66, 1.52 (H6,7), 1.51 (H9), 1.44 (BCH_3)

12: $\delta^{11}B$ 46.4, 37.6; $\delta^{27}Al$ 103.7, $h_{(1/2)}$ 25 Hz; δ^1H 1.97 (H2—4), 1.72, 1.56 (H6,7), 1.34 (H9), 7.52—7.70 (BC_6H_5)

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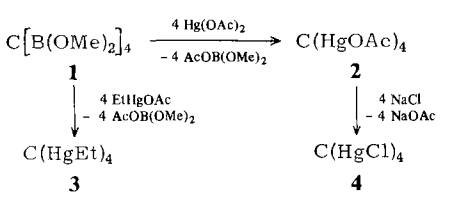
Tetralithiomethane**

By *Adalbert Maercker** and *Manfred Theis*

Tetralithiomethane **5** was first described by *Lagow* et al.[1] who were able to generate it in a maximum yield of 40.5% (detected as CD_4 in addition to other deuterated products) by reaction of tetrachloromethane and lithium vapor. The major side product in this reaction is lithium carbide in addition to traces of perlithioethene and perlithioethane. An increase of the reaction temperature from 750 to 800 °C reduces the yield of CLi_4 to 14% in favor of perlithioethene.

Lagow et al.[2] have also investigated the pyrolysis behavior of tetralithiomethane, reporting that the compound is thermolabile referred to decomposition into lithium carbide via perlithioethene and perlithiopropyne.

By analogy to previously published procedures for the synthesis of polylithiated hydrocarbons[3,4] bearing several Li atoms on one C atom ("isocentric"), we have now found two further methods of generating **5**. Reaction of octamethyl methanetetraboronate **1**[5] with mercury(II) acetate affords tetrakis(acetoxymercurio)methane **2**, which in turn can be converted by sodium chloride into tetrakis(chloromercurio)methane **4**[6,7]. If instead of mercury(II) acetate, ethylmercury acetate is employed, tetrakis(ethylmercurio)methane **3** is obtained, an approach based on the synthesis of the corresponding methyl compound developed by *Breitinger* and *Kress*[9].



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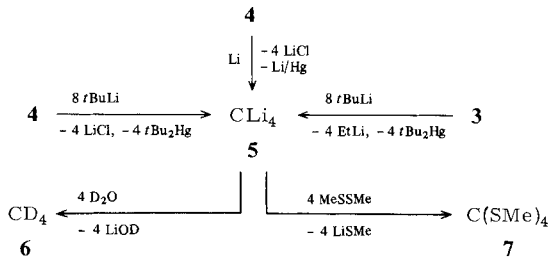
[**] Polylithiumorganic Compounds. Part 3. This work was supported by the Fonds der Chemischen Industrie. We thank Prof. Dr. *D. Breitinger* and Prof. Dr. *P. v. R. Schleyer*, Erlangen, for discussions.—Part 2: [4].

Reaction of **4** with lithium dust in diethyl ether using the method described in [3] leads within 3 h to a black suspension, which, following standard and inverse deuteriolysis, affords comparatively little tetradeuteriomethane in addition to predominantly tetradeuterioethene and hexadeuterioethane[10]. Interestingly, this product distribution is qualitatively in accord with that described by *Lagow* et al.[1], and is attributable to dimerization of radical intermediates.

Because of the atypical reaction behavior of isocentric polylithiated hydrocarbons with anion trapping reagents, derivatization with chlorotrimethylsilane/tetrahydrofuran leads to a large number of substances, among which tetrakis(trimethylsilyl)methane is present only in $<5\%$.

Much better results are obtained if excess *tert*-butyllithium is used for the transmetalation of **4** as previously described for analogous compounds[3,4]. In this case, the transmetalation mechanism changes from radical to ionic and, hence, no coupling products arise. In cyclopentane, an amalgam-free, insoluble product, which still contains lithium chloride, is formed; after the product had been filtered and freed from adherent di-*tert*-butylmercury it was deuteriolyzed for the qualitative determination of **5**. Apart from traces of dideuterioacetylene, the reaction gases contained only tetradeuteriomethane **6**, which, however, could not be separated by gas chromatography from the argon used as inert gas atmosphere. Here, again, silylation proceeded unsatisfactorily.



Use of **3** instead of **4** as substrate and of at least stoichiometric amounts of *tert*-butyllithium in cyclopentane yields, after stirring for one day at room temperature, a deep red-brown *solution*, whose deuteriolysis furnishes **6** and traces of dideuterioacetylene as derivatives; these arise directly or indirectly from CLi_4 **5**. Additionally, as a major product the reaction gas contains CH_3CH_2D (from EtLi) and, occasionally, $(CH_3)_3CD$ (from excess *t*BuLi). In contrast, silylation again proceeds unsatisfactorily.

The particular demands of polylithioalkanes on a derivatization reagent are apparently met by dimethyl disulfide. Hence, the dark colored solutions can be quasi-titrated with dimethyl disulfide in hexane at $-50\,^{\circ}C$. Work-up afforded quantitative crude yields of tetrakis(methylthio)methane **7** (m.p. = 36—40 °C), which after two recrystallizations from ethanol melted at 64 °C (m.p. = 65 °C[11]). Under these conditions **3** and **4** do not react with dimethyl disulfide; in contrast, *tert*-butyllithium reacts more rapidly with dimethyl disulfide than with **3** or **4**.

^{13}C- and ^{6}Li-NMR spectroscopic studies of solutions of ^{6}Li-labeled **5** in [D_{12}]cyclohexane did not provide reliable results, because of accompanying substances (EtLi, tBu_2Hg, *t*BuLi), the low concentration of CLi_4, and the expected low sensitivity of this carbon atom (high multiplicity, absence of NOE). A qualitatively very good product **5**—a deep red-brown, extremely pyrophoric *solid*—is obtained if the solvent and readily volatile and sublimable accompanying products are removed[12]. The original solution presumably contained a complex of CLi_4 **5** and di-*tert*-butylmercury, particularly since the solutions are highly light-sensitive (more sensitive than tBu_2Hg) and the fact that **5** no longer dissolves in hexane after removal of tBu_2Hg.

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[2] L. A. Shimp, J. A. Morrison, J. A. Gurak, J. W. Chinn, Jr., R. J. Lagow, *J. Am. Chem. Soc. 103* (1981) 5951.
[3] A. Maercker, M. Theis, A. J. Kos, P. von R. Schleyer, *Angew. Chem. 95* (1983) 755; *Angew. Chem. Int. Ed. Engl. 22* (1983) 733.
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[5] R. B. Castle, D. S. Matteson, *J. Organomet. Chem. 20* (1969) 19.
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[7] D. Breitinger, W. Morell, K. Grabetz, *Z. Naturforsch. B 34* (1979) 390.
[8] Obtained by comproportionation of mercury(II) acetate and diethylmercury in methanol at room temperature; crystallized at $-30\,^{\circ}C$ from methanol.
[9] W. Kress, Dissertation, Universität Erlangen-Nürnberg 1983.
[10] The extent of conversion was determined gravimetrically as over 80% from the mercury precipitated.
[11] H. Böhme, G. Ahrens, *Liebigs Ann. Chem. 1982*, 1022.
[12] *Procedure:* Thoroughly dry **3** (0.93 g, 1 mmol) is added portionwise to 10 mmol of a 0.25 M solution of *tert*-butyllithium under argon, a large batch of which was prepared previously from di-*tert*-butylmercury and lithium (molar ratio 1:10) in cyclohexane, and the mixture stirred for 24 h at room temperature in the dark. The deep red-brown solution is transferred to a sublimation apparatus with argon inlet and frozen using liquid nitrogen. Subsequently the apparatus is evacuated to 10^{-3} torr, the external cooling source removed, and the distilled solvent collected in a cold trap. After removal of all the solvent from the mixture, the solid residue is heated in the dark to 100 °C, whereupon the side products di-*tert*-butylmercury and ethyllithium as well as excess *tert*-butyllithium sublime out at 10^{-3} torr. A deep red-brown, extremely pyrophoric residue of CLi_4 **5** remains. For derivatization, this product is suspended in 5 mL hexane and treated with a solution of dimethyl disulfide (0.5 g, 5.32 mmol) in 5 mL hexane at $-30\,^{\circ}C$ with stirring. The mixture is allowed to warm to room temperature, the lithium thiomethanolate is filtered off, and the filtrate concentrated to dryness using a water pump. 0.16 g (80%) **7** is obtained (m.p. = 50—54 °C), which after two recrystallizations from ethanol melts at 63—64 °C (m.p. = 65 °C [11]).

Biosynthesis of Moniliformin, A Fungal Toxin with Cyclobutanedione Structure**

By *Burchard Franck** and *Gerhard Breipohl*

The mycotoxin moniliformin **1**[1] is formed in high concentrations[2] by the maize fungi *Fusarium moniliforme* and *Gibberella fujikuroi*. Because of its intense toxicity[3], high acidity ($pK_a = 0.88$[4]), and structural relationship with squaric acid **2**, compound **1** is particularly important. We now report on incorporation experiments which throw light on the biogenesis of **1**.

We considered three hypotheses for the biosynthesis of **1**: 1) cyclization and further conversion of erythrose **5**; 2) condensation of two acetate moieties via malonyl coen-

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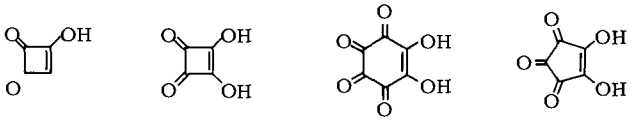
[**] Biologically Active Substances from Fungi, Part 34. This work was supported by the Minister für Wissenschaft und Forschung des Landes Nordrhein-Westfalen as well as by the Fonds der Chemischen Industrie.—Part 33: B. Franck, *Angew. Chem. 96* (1984) 462; *Angew. Chem. Int. Ed. Engl. 23* (1984) 493. Part 32: B. Franck, A. Stange, *Liebigs Ann. Chem. 1981*, 2106.

zyme A **8** to afford 1,3-cyclobutanedione **9**, followed by oxidation to the tautomeric derivatives **10a**—**10c**, and dehydration; 3) biosynthesis from inositol **7** via rhodizonic acid **3** and croconic acid **4**[5,6].

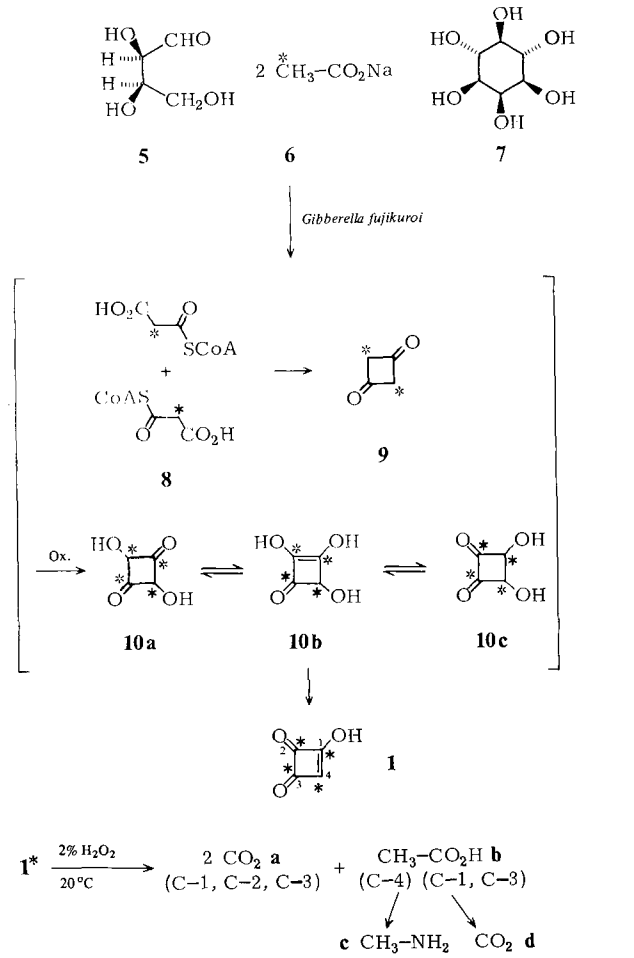


1 **2** **3** **4**

To test these hypotheses, we applied [1-^{14}C]erythrose **5**, [2-^{14}C]acetate **6**, and [U-^{14}C]inositol **7**, respectively, to four cultures of *G. fujikuroi* (ATCC 12763) growing on a maize solid nutrient medium (50 g maize, 70 mL water). After 7—14 d the fungal mycelia were freeze-dried and extracted with MeOH. **1** was separated off on an anion exchanger (Dowex AG 1 X2) and recrystallized from methanol to constant radioactivity as the sodium salt dihydrate.

Table 1. Incorporation studies on the biosynthesis of monoliformin **1**.

Precursor	Spec. radioact. [mCi/mmol]	Isolated **1*** Amount [mg]	Spec. ratioact. [nCi/mmol]	Spec. incorp. rate [%]
[1-^{14}C]Erythrose **5**	0.667	18.5	263	0.039
[2-^{14}C]Acetate **6**	0.146	145	514	0.180
[U-^{14}C]Inositol **7**	278	75.2	8.36	4.5×10^{-6}



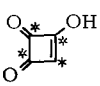
5 **6** **7** **8** **9**

Scheme 1. Precursors, biosynthesis and degradation of moniliformin **1**.

According to the results in Table 1, compounds **5** and **7** can be ruled out as biosynthetic precursors of **1**. Similarly, [U-^{14}C]glucose, [U-^{14}C]erythritol, [U-^{14}C]asparagine, [U-^{14}C]pyruvate, [U-^{14}C]shikimic acid, [β-^{14}C]cinnamic acid, [U-^{14}C]phenylalanine, and [methyl-^{14}C]methionine exhibited no significant incorporation. In contrast, [2-^{14}C]acetate **6**, although it is involved in numerous metabolic pathways, exhibits a specific incorporation rate of 0.18% and is, hence, a precursor of **1**. Of the large group of natural products formed by cyclization of polyketides, **1** is therefore the first example derived from a diketide $[CH_3\text{-}CO\text{-}CH_2\text{-}]_nCO_2H$, n = 1].

To gain some insight into the *course of the biosynthesis*, we studied the isotopic distribution in moniliformin **1*** obtained using **6** as precursor (Scheme 1). H_2O_2-Oxidation of moniliformin **1*** diluted with inactive **1** to 130000 dpm/mmol[7] afforded, apart from CO_2 **a** from C-1, C-2, and C-3, radiolabeled acetic acid **b**. In **b** the radioactivity of the methyl group originates from C-4 and that of the carboxy groups in equal parts from C-1 and C-3 of **1***. The distribution of radioactivity (Table 2) in these degradation products as well as that in the products CO_2 **d** and methylamine **c** obtained by chemical degradation of the acetic acid **b** corresponds to a moniliformin in which the radioactivity is distributed over all C atoms and not only over C-2 and C-4. This result is consistent with an equilibrating intermediate **10a**—**10c** having four oxygen substituents.

Table 2. Distribution of radioactivity in the degradation products of moniliformin **1*** from the biosynthetic experiments (cf. Scheme 1).

Product	Spec. Radioact. (dpm/mmol)	Radioactive C atoms Found[a]	calc. for 	calc. for
1*	130000	2	2	2
CO_2 **a**	39000	0.61	0.5	0.5
Acetic acid **b**	66000	1.02	1.0	1.0
Methylamine **c**	32000	0.49	0.5	1.0
CO_2 **d**	32600	0.50	0.5	0

[a] For determination of the number of radioactive C atoms *found* in **1***, the specific radioactivities of the degradation products were divided by those of **1*** and multiplied by 2.

Because of the uniform distribution of radioactivity in the moniliformin **1*** obtained using [2-^{14}C]acetate nutrient, it could be argued that the acetate moieties are not incorporated directly, but rather via an indirect route. In this case the specific incorporation rate would, however, be considerably less than the value found (0.18%). We have observed a similar equipartition of the radioactivity in a total synthesis of **1*** from [1-^{14}C]acetate modelled on the biosynthesis.

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1, 52591-22-7; **6**, 64-19-7

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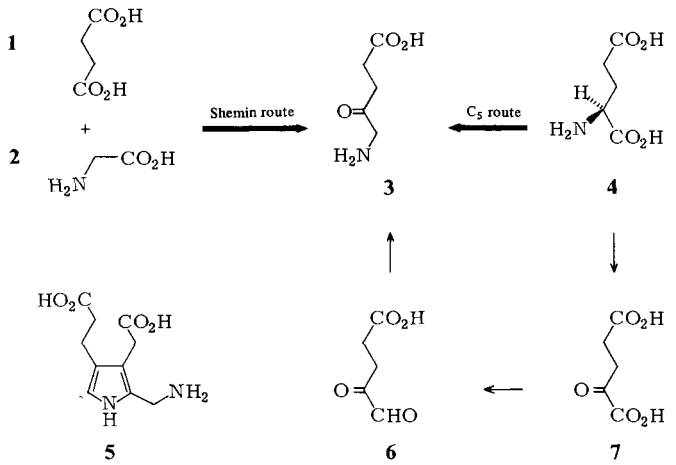
[7] dpm = disintegrations per minute.
[8] A. Löbberding, Dissertation, Universität Münster 1983.

Heme Biosynthesis from L-Glutamic Acid**

By *Burchard Franck*, Manfred Bruse,* and *Jürgen Dahmer*

Textbooks of chemistry and biochemistry state that the red blood pigment heme **8** is synthesized in higher organisms from succinic acid **1** and glycine **2**. The two last-mentioned compounds initially react to form 5-aminolevulinic acid **3**, two molecules of which condense to afford the heme building block porphobilinogen **5**[1]. In contrast to this *Shemin route*[2], the large amounts of 5-aminolevulinic acid **3** required in plants for the biosynthesis of chlorophylls are principally formed via a C_5 *route* from L-glutamic acid **4**[3] via 2-oxoglutaric acid **7** and 4,5-dioxovaleric acid **6**. We now report on incorporation experiments which indicate that the C_5 route is also involved to a considerable extent in animal organisms.



For the purpose of this study, we employed the enzyme system obtained from duck blood[4] (which was also used to prove the Shemin route of heme biosynthesis). Three important requirements had to be met:

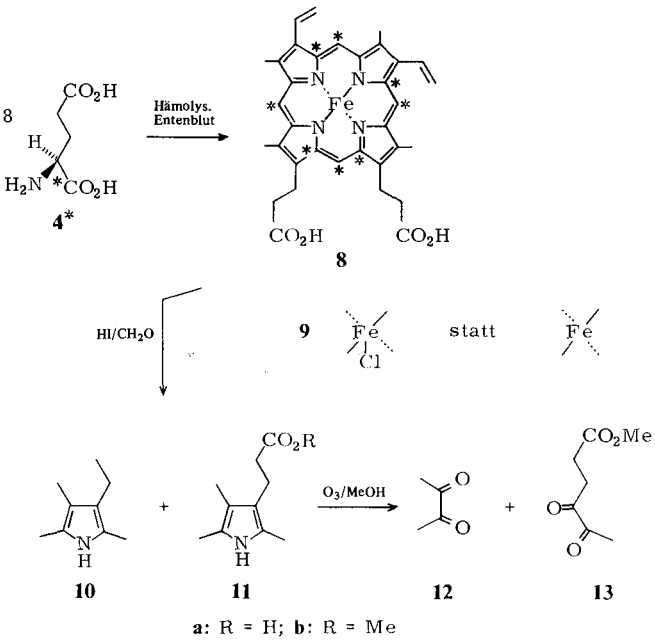
1) *Reproducibility:* The incorporation experiments with hemolyzed duck blood[4] were repeated several times over three years, systematically varying the season the blood was taken, the concentration, and the incubation time.

2) *Exclusion of the possibility that incorporation of 4 is not feigned by its degradation to 1:* Use of [1-^{14}C]-L-glutamic acid **4***, whose labeling would be eliminated upon decarboxylation to **1**.

3) *Proof that 4 is incorporated directly:* Determination of the labeled positions in the product of the biosynthetic heme **8** by chemical degradation.

Table 1. Comparison of the results of incorporation studies on the biosynthesis of the red blood pigment heme **8**.

Precursor	Precursor Amount [μmol]	Precursor Total radioact. [μCi]	Isolated hemin **9** Total radioact. [nCi]	Isolated hemin **9** Absolute incorp. rate [5] [% × 10^3]
[2-^{14}C]glycine **2**	0.96	50	14.7	29.5
[1,4-$^{14}C_2$]succinic acid **1**	0.86	100	8.04	8.04
[1-^{14}C]L-glutamic acid **4***	1.01	50	3.74	7.49



75 mL Hemolyzed duck blood[4] was incubated for 24 h with 1 μmol of each of the radioactive precursors; the hemin **9** isolated was purified by recrystallization to constant radioactivity. Table 1 summarizes the data obtained from the various mixtures. The absolute incorporation rates proved to be independent of further increase in incubation time.

The value of the absolute incorporation rate for [2-^{14}C]-glycine **2** provides a measure for the biosynthesis of 5-aminolevulinic acid **3** by the Shemin route. The incorporation rate of [1-^{14}C]L-glutamic acid **4*** indicates that the C_5 route is involved to 25.4%. Relative to the incorporation of [1,4-$^{14}C_2$]succinic acid **1** (Shemin route), the extent of glutamic acid incorporation and the C_5 route are even larger.

Upon *direct* incorporation of **4***, its radioactive C atoms should distributive over the eight C atoms of heme **8** marked with a cross. In order to prove this, the radioactive hemin **9** obtained was degraded in two steps[6]. Cleavage with HI/CH_2O yielded phyllopyrrole **10** and phyllopyrrolecarboxylic acid **11a**; the latter compound was esterified to **11b** with diazomethane. Ozonolysis of **11b** afforded 2,3-butanedione **12** (analyzed as dioxime) and methyl 4,5-dioxohexanoate **13**. The specific radioactivities of the degradation products (Table 2) correspond to the values cal-

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[**] Tetrapyrrole Biosynthesis, Part 17. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.—Part 16, [1]. Part 15: B. Franck, W. Bock, U. Wolters, *Angew. Chem. 94* (1982) 226; *Angew. Chem. Int. Ed. Engl. 21* (1982) 215.

Table 2. Distribution of radioactivity in the radioactive hemin **9** and its degradation products **10**—**13** obtained by incorporation of [1-^{14}C]L-glutamic acid **4***.

Products	Spec. radioact. [a] [nCi/mmol]	Found	Radioactive C atoms [b] Calc. for direct incorporation	Calc. for equipartition
9	3.29	8	8	8
10	0.761	1.87	2	1.88
11b	0.745	1.82	2	2.12
12	0.190	0.46	0.5	0.82
13	0.610	1.48	1.5	1.29

[a] Mean value of two independently performed degradation sequences in which the relative deviation from the mean value was less than 1%. [b] For the determination of the number of radioactive C atoms *found*, the specific radioactivities of all the products were divided by those of hemin **9** and multiplied by 8.

culated for the direct incorporation of **4*** and differ significantly from those for equipartition of the ^{14}C atoms over the heme molecule.

According to the results reported here, in animal organisms there exists a particularly straightforward *second route* for heme biosynthesis starting from eight molecules of the ubiquitous L-glutamic acid **4**.

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1, 110-15-6; **2**, 56-40-6; **3**, 106-60-5; **4**, 56-86-0; **8**, 14875-96-8; **9**, 16009-13-5

[1] B. Franck, *Angew. Chem. 94* (1982) 327; *Angew. Chem. Int. Ed. Engl. 21* (1982) 343.

[2] D. Shemin, D. Rittenberg, *J. Biol. Chem. 166* (1946) 621; N. S. Radin, D. Rittenberg, D. Shemin, *ibid. 184* (1950) 745.

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[5] The total radioactivity of the isolated, radioactive hemin **9** divided by that of the ^{14}C-labeled precursor × 100. As a consequence of the participation of this precursor in competing metabolic pathways, particularly in protein biosynthesis, its incorporation rates are relatively low, as observed in similar studies [2]; however, in our case they lie > 10 fold above the significance level.

[6] Cf. [4b, c] and literature cited therein. Isolation of **12** and **13** in the molar ratio 1:1 can be ascribed to induction of the 2*H*-pyrrole structure upon electrophilic attack of ozone.

A Novel Double-Stacked Structure in Bis[(oxamide oximato)(oxamide oxime)platinum(II)]-[{tris(tetracyanoquinodimethane)}diide], a Molecular Electron Conductor**

By *Helmut Endres**

"Organic metals" contain stacks of planar radical ions with a fractional average charge per molecule[1]. In some solids containing organic radical cations and simple inorganic counterions, even superconductivity is observed[2]. The radical anion of tetracyanoquinodimethane ["tcnq", 2,2'-(2,5-cyclohexadien-1,4-diylidene)bispropanedinitrile] is a frequently used component of electrically conducting molecular solids[1]. We have already reported on the salt **1**, the first solid consisting of segregated, parallel, regularly stacked planar complex cations and organic radical anions[3]. As is to be expected it is a semiconductor, whereas the analogous Ni-compound is metallic at room temperature and consequently in this case, we assume a fractional average charge per molecule[4].

$[Pt(oaoH)(oaoH_2)]^{\oplus}tcnq^{\ominus}$ **1**
$oaoH_2$ = oxamide oxime, $HON{=}C(NH_2){-}C(NH_2){=}NOH$

$\{[Pt(oaoH)(oaoH_2)]^{\oplus}\}_2(tcnq)_3^{2\ominus}$ **2**

The title compound **2**, which is formed as a byproduct on growing crystals of **1**[5], clearly contains tcnq species with different charges. As in the case of **1**, the growth of the crystals is associated with the shift of the equilibrium in the protolysis

$$[Pt(oaoH_2)_2]^{2\oplus} \rightleftharpoons [Pt(oaoH)(oaoH_2)]^{\oplus} + H^{\oplus}$$

to the right. In addition, $tcnq^{\ominus}$ is partially oxidized to neutral tcnq, some of which crystallizes out, and is partly used in the formation of **2**. The X-ray structure analysis[6] shows the presence of an unusual double-stacked structure (Fig. 1): The crystals contain pure tcnq stacks, whereby it can be

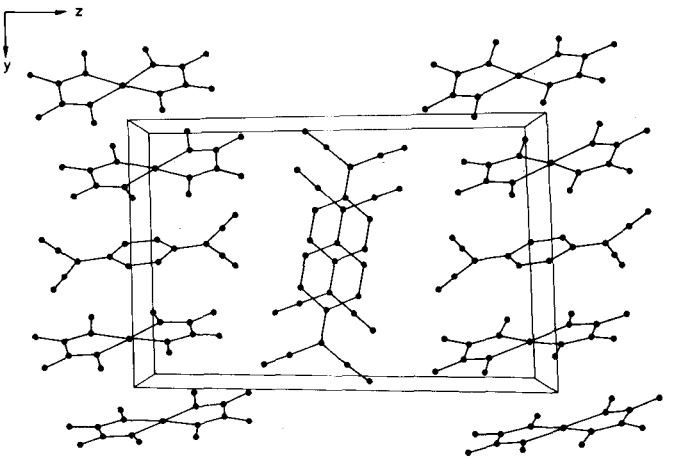

Fig. 1. Projection of the structure of **2** along the $tcnq^{\frac{1}{2}\ominus}$ stack.

estimated from the bond lengths (Fig. 2)[7] that the (crystallographically equivalent) tcnq units of the stack carry an average charge of $-1/2$. Hence, both criteria for metallic behavior—pure stack and fractional charge—are fulfilled. The d.c. conductivity at room temperature is 12 Ω^{-1} cm^{-1}[8]; more detailed investigations of the transport properties are under way. A surprising feature is that the tcnq molecules form a zig-zag arrangement along the stack (Fig. 3), as is typical for the radical cation stacks of some organic superconductors[2b], but is rarely to be found in tcnq salts.

Perpendicular to the tcnq stacks there is a second type of stacking (Fig. 1): mixed stacks of two complex cations and one $tcnq^{\ominus}$ anion with full negative charge. Mixed stacks of this kind occur more frequently than segregated stacks in charge transfer complexes[1], even though the observed sequence (one acceptor after each two donors) is rare. Such stacks do not lead to high electrical conductivity. The title compound **2**, in which pure stacks and mixed stacks are arranged perpendicularly to each other, represents a novel type of structure for molecular electron conductors.

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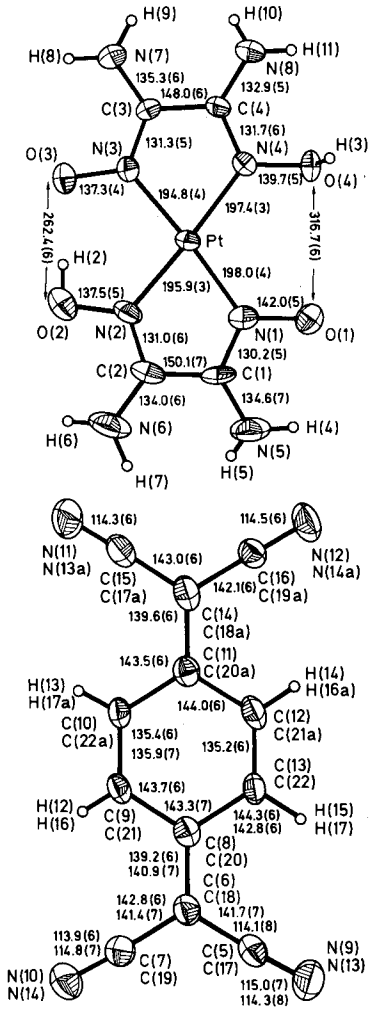

Fig. 2. Bond lengths [pm] in the complex cation (top) and in the tcnq anions (bottom). In the case of the anions the upper value applies for the $tcnq^{\frac{1}{2}\ominus}$ ion of the pure stack, the lower one for the $tcnq^{\ominus}$ ion of the mixed stack.

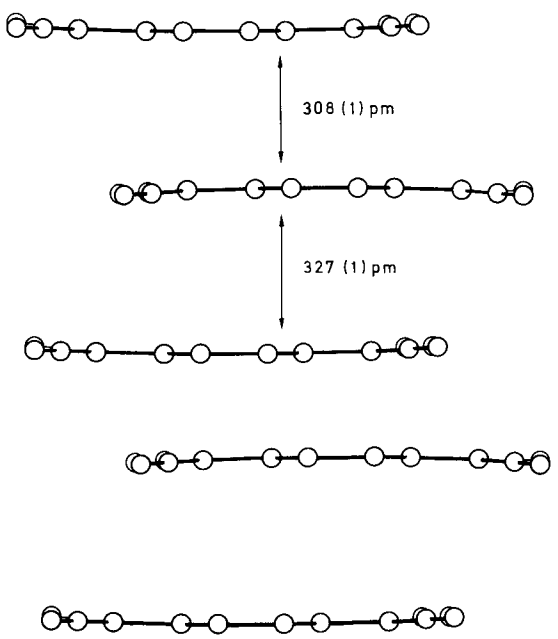

Fig. 3. View of the $tcnq^{\frac{1}{2}\ominus}$ stack perpendicular to the direction of stacking.

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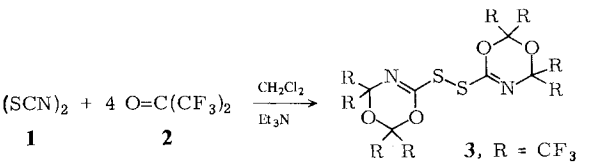
[1] a) J. B. Torrance, *Acc. Chem. Res. 12* (1979) 79; b) P. Delhaes, *Mol. Cryst. Liq. Cryst. 96* (1983) 229.
[2] a) T. Mori, A. Kobayashi, Y. Sasaki, H. Kobayashi, G. Saito, H. Inokuchi, *Chem. Lett.*, in press; b) K. Bechgaard, K. Carneiro, F. B. Rasmussen, M. Olsen, G. Rindorf, C. S. Jacobsen, H. J. Pedersen, J. C. Scott, *J. Am. Chem. Soc. 103* (1981) 2440.
[3] H. Endres, *Angew. Chem. 94* (1982) 548; *Angew. Chem. Int. Ed. Engl. 21* (1982) 524; *Angew. Chem. Suppl. 1982*, 1309.
[4] H. Endres, A. Bongart, D. Nöthe, I. Hennig, D. Schweitzer, H. Schäfer, H. W. Helberg, S. Flandrois, *Z. Naturforsch. B*, in press.
[5] Crystal growth: A solution of Li(tcnq) in 1-butanol was covered with a solution of $[Pt(oaoH_2)_2]Cl_2$ in methanol in a test-tube. Needle-shaped crystals of **1** were gradually formed in large amount and, after a few days, also single crystals of **2**, which were easily differentiated by their platelet-like shape.
[6] Triclinic, $P\bar{1}$, $a=636.04(7)$, $b=1117.3(2)$, $c=1743.3(2)$ pm; $\alpha=87.98(1)$, $\beta=80.21$, $\gamma=87.14(1)°$, $V=1219\times10^6$ pm^3, $Z=1$, $\rho_{calc}=2.01$ g cm^{-3}, $\mu_{calc}=58.8$ cm^{-1}; monochromated $Mo_{K\alpha}$ radiation, 7300 observed ($I>3\sigma(I)$), independent, empirically absorption-corrected reflections, $R_w(R)=0.036$ (0.040) with 16 of the 17 symmetry-independent H atoms included. Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD 51090, the names of the authors, and the journal citation.
[7] S. Flandrois, D. Chasseau, *Acta Crystallogr. B33* (1977) 2744.
[8] I. Hennig, D. Schweitzer, private communication.

Dithiocyanogen Reaction without Cleavage of the S–S Bond: Cycloaddition with Hexafluoroacetone**

By *Herbert W. Roesky**, *Nayla K. Homsy*, *Mathias Noltemeyer*, and *George M. Sheldrick*

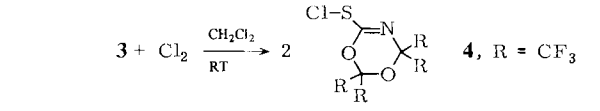
Dedicated to Professor Kurt Issleib on the occasion of his 65th birthday

Dithiocyanogen **1**, first described in 1919 by *Söderbäck*[1], shows the characteristic reactions of a pseudohalogen and serves as a universal reagent for the synthesis of thiocyanates; the reactions proceed with cleavage of the sulfur-sulfur bond. We report here on the cycloaddition of **1** with hexafluoroacetone **2**, which leads to formation of the 4*H*-dioxazine derivative **3** in 82% yield[2].



An X-ray structure analysis of **3** (colorless solid, m.p. 50–51°C) revealed that two 4*H*-dioxazine rings are coupled via a disulfide bridge in such a way that the molecule has an almost twofold symmetry axis perpendicular to the S–S bond (see Fig. 1). The S–S bond length is 202.0(2) pm, the C–S–S–C torsion angle −86.6(2)°.

3 can be cleaved at the S–S bond by chlorine to give the sulfenic acid chloride **4** (45% yield, yellow liquid, b.p. 69°C/64 mbar).



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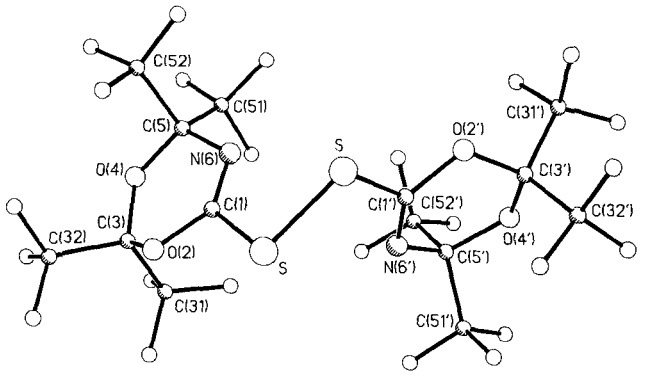
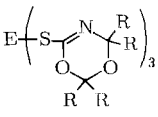


Fig. 1. Structure of **3** in the crystal. Crystal data: space group $P2_1/c$, $a=1290.3(5)$, $b=1362.8(7)$, $c=1416.8(6)$ pm, $\beta=95.76(3)°$, $Z=4$, $R=0.044$ for 2295 independent reflections with $F>4\sigma(F)$; $Mo_{K\alpha}$ radiation, $2\theta_{max}=45°$. The structure was solved by direct methods and anisotropically refined. The assignment of nitrogen and oxygen [O(2)/N(6), O(2')/N(6')] was carried out on the basis of the thermal parameters and bond lengths. Selected bond lengths: C–S 175.9(6), C=N 125.0(6), N–C 142.3(6), C–O 139.7(9), C–C 154.1(7), and C–F 131.7(7) pm. Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD 51 129, the names of the authors, and the journal citation.

Cycloaddition also takes place on reaction of $S(SCN)_2$ $Hg(SCN)_2$, $P(NCS)_3$ or $As(NCS)_3$ with hexafluoroacetone[3]. The novel compounds thus formed are crystalline, some of which could be characterized by X-ray structure analysis[3]. $P(NCS)_3$ and $As(NCS)_3$ probably first isomerize to $P(SCN)_3$ and $As(SCN)_3$ before they form the adducts **5** and **6** with hexafluoroacetone.



5, E = P, R = CF_3
6, E = As, R = CF_3

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CAS Registry numbers:
1, 505-14-6; **2**, 684-16-2; **3**, 93383-94-9; **4**, 93383-95-0; **5**, 93383-99-4; **6**, 93384-00-0; $S(SCN)_2$, 57670-85-6; $Hg(SCN)_2$, 592-85-8; $P(NCS)_3$, 1858-23-7; $As(NCS)_3$, 93383-96-1; $S(SC{=}NC(CF_3)_2OC(CF_3)_2O)_2$, 93383-97-2; $Hg(SC{=}NC(CF_3)_2OC(CF_3)_2O)_2$, 93383-98-3; Et_3N, 121-44-8; Cl_2, 7782-50-5

[1] E. Söderbäck, *Justus Liebigs Ann. Chem. 419* (1919) 217.
[2] Procedure and spectroscopic data: $(CF_3)_2CO$ (36.7 g, 221 mmol) and a catalytic amount of Et_3N were condensed with a solution of $(SCN)_2$ (5.1 g, 44 mmol) in CH_2Cl_2 (100 mL) at $-196°C$. The yellow solution was stirred for 2 h at room temperature and then concentrated. The pale yellow residue was filtered off, vacuum dried (28 g, 82%), and recrystallized from CH_2Cl_2.—^{19}F-NMR (C_6F_6, 60 MHz): $\delta=82.5$, 83.6 (CF_3, septets); ^{13}C-NMR ($CDCl_3$, 62.9 MHz): $\delta=159.3$ (C=N, singlet), 119.1, 118.4 (CF_3, quartets, $^1J_{CF}=288.6$ and 290.0 Hz), 92.8 (O–C–O, septet, $^2J_{CF}=36.8$ Hz), 84.7 (O–C–N, septet, $^2J_{CF}=34.6$ Hz); IR (KBr): 1670 ($\nu_{C=N}$), 1130–1330 cm^{-1} (ν_{CF_3}); Raman: 132 (s), 186 (w), 282 (m), 334 (m), 738 (w), 780 (vs), 1678 cm^{-1} (vs); FI-MS: *m/z* 780 (100%, $M^{\oplus}$); EI-MS: *m/z* 780 (100%, $M^{\oplus}$), 761 (39%, $M^{\oplus}-F$), 711 (37%, $M^{\oplus}-CF_3$), 545 (28%, $M^{\oplus}-HFA-CF_3$), 422 (50%, $M^{\oplus}-2HFA-CN$), 353 (11%, $M^{\oplus}-2HFA-CN-CF_3$) (HFA = hexafluoroacetone).
[3] N. K. Homsy, V. W. Pogatzki, J. Lucas, unpublished.

BOOK REVIEWS

Organometallic Chemistry of Rhodium and Iridium by *Ronald S. Dickson*, Academic Press, New York 1983. x, 421 pp., bound, $ 85.00.—ISBN 0-12-215480-0.

This book is a volume in the Series "Organometallic Chemistry" edited by *P. M. Maitlis, F. G. A. Stone*, and *R. West*. It contains a comprehensive discussion of the organometallic chemistry of Rhodium and Iridium. The literature has been covered to the end of 1978, while some key references for 1979 and 1980 are also included.

Anyone working in this field will realize the enormous amount of work which has been involved in the writing of this book. It has, however, been a worthwhile task, not only because of the author's thoroughness but also since the organometallic chemistry of rhodium and iridium has been and still is of central importance for a great variety of disciplines and diverse fields, such as organic chemistry and catalysis.

In addition to a short general introduction to the chemistry of rhodium and iridium, the book contains chapters on carbonyl compounds and their substitution products, carbonyl-halide and carbonyl-hydride complexes, complexes involving thiocarbonyl, trifluorphosphane, isonitrile and aryldiazo ligands, organorhodium and organoiridium complexes, complexes formed from alkynes and finally σ-alkyl, σ-aryl and related complexes. There is a reference list containing more than two thousand references, an addendum containing an extensive list of key references, and a subject index.

It is clear that with a book containing so many references the treatment of each subject necessarily has to be superficial. Nevertheless, the literature is so well covered, as I have checked myself for a great number of references, that the book may be used as an excellent reference work to the original literature—and this is of enormous importance particularly when dealing with the chemistry of rhodium and iridium. The book, however, is more than a reference work only, since the author has succeeded well in presenting the material in a logical way useful to the reader who wishes to gain a broad idea of what has been done in the various fields covered. He has also attempted to present, where possible, the bonding theories involved, such as for example the electronic structures of carbonyl cluster complexes. Again such treatments are not discussed in depth, but are sufficient for the interested reader to find his own way in the original literature.

Finally, it should be mentioned that this book presents in a very concise and clear way the vast amount of research that was carried out in the sixties and seventies. Furthermore, I would like to emphasize the fact that I have found very few errors, even in the printing itself; this is undoubt-

edly due to the thorough editing which is characteristic for the books in this series. It is to be hoped that a follow up of this work will appear in the future covering the more recent literature.

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Lecture Notes in Chemistry. Vol. 34: Unified Valence Bond Theory of Electronic Structure. Applications. By *N. D. Epiotis*. Springer-Verlag, Berlin 1983. viii, 585 pp., paperback, DM 96.00.

The complete work by *Epiotis* on the theory of chemical reactivity deserves a great deal of respect: it is exemplary, comprehensive, of wide applicability, and eschews traditional viewpoints. The author considers the most widely referred to quantum chemical method, the qualitative one-determinant MO method, as being insufficient and exploits, in a skillful way, the positive features of both fundamental quantum chemical techniques, namely the molecular orbital and the valence bond methods. His procedure permits analysis of a wide spectrum of diverse problems concerning chemical reactivity in the electronic ground state and in the excited state. The theoretical foundation of the Epiotis procedure formed the subject of the 29th volume of the Series. With this procedure, relationships can be brought to light which at first are unexpected or at least not obvious. The scope of application of the theory is very broad. This is reflected in the titles of the chapters; for example: Why do organolithium monomers have strange structures? Conformational isomerism of N_2H_4 and its derivatives. Saga of "hypervalent" molecules. Why benzene prefers to substitute and an olefin likes to add? Frontier configuration and a new classification of annulenes. The qualitative rationalization and prediction of "correlation effects" in "complex" ground state molecules. The author analyses these and numerous other problems in a way which has some formal resemblance to the procedures of *Woodward* and *Hoffmann, Longuet-Higgins,* and *Abrahamson,* but the level of sophistication is higher and it corresponds to the level of configuration interaction. All these features are, no doubt, very attractive.

I am afraid, however, that in spite of all the positive features, attempts to exploit the Epiotis theory can meet with serious difficulties. Namely, I expect that it will not be easy to convince chemists not only to read about the new procedure but also to master it in order to make proper use of it. I am afraid that even for good chemists who are open-minded towards new theories it would be too laborious. Admittedly, chemists have been able to manage even more involved concepts and theories; however, these frequently offer numerical values useful for correlations or even for calculating absolute values of physical characteristics. On the other hand simple, cheap, and efficient tools introduced by *Woodward* and *Hoffmann* and by *Fukui* are also reliable and widely applicable (though not as widely as the present theory). But in spite of the above-mentioned feeling the Epiotis procedure does represent an important contribution: do not hesitate to read it.

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and Electrochemistry,
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New Books

The following books have been received by the editor. All the publications listed are available through W & P Buchversand für Wissenschaft und Praxis, Boschstrasse 12, D-6940 Weinheim (Federal Republic of Germany). Tel. (06201) 606-0, Telex 465516 vchwh d, Telefax (06201) 602328.

A Manual of Chemical and Biological Methods for Seawater Analysis. By *T. R. Parsons, Y. Maita, C. M. Lalli.* Pergamon Press, Oxford 1984. xiv, 173 pp., Paperback, $ 8.95.—ISBN 0-08-030287-4

Reactive Molecules. The Neutral Reactive Intermediates in Organic Chemistry. By *C. Wentrup.* John Wiley, Chichester 1984. xi, 333 pp., bound, £ 33.20.—ISBN 0-471-87636-9

Molecular Diffusion and Spectra. By *W. T. Coffey, M. W. Evans,* and *P. Grigolini.* John Wiley, Chichester 1984. viii, 378 pp., bound, £ 47.50.—ISBN 0-471-87539-2

Oxygen and the Conversion of Future Foodstocks. Third BOC Priestley Conference. The Royal Society of Chemistry, London 1984. viii, 471 pp., Paperback, £ 18.00 (reduction for members of the Royal Society of Chemistry)—ISBN 0-85186-915-7

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